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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "Preparation and Properties of Some Cyclic Hydroxylamines" submitted by Abdel-monaem M. K. El-hawari in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Date JAN 15 1974

THE UNIVERSITY OF ALBERTA

PREPARATION AND PROPERTIES OF SOME CYCLIC HYDROXYLAMINES

by

© ABDEL-MONAEM M. K. EL-HAWARI

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

FACULTY OF PHARMACY AND
PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA
SPRING, 1974

TO SOHA

ABSTRACT

The primary objective of the present study was to prepare some novel cyclic hydroxylamines and to study their chemical and pharmacological properties. Cyclic hydroxylamines have recently been shown to be metabolites of certain cyclic secondary amines. Little is known of their pharmacological properties.

Reductive cyclization of three 4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-ones by means of sodium borohydride and palladium-charcoal gave mainly spiro (1-hydroxyindoline)-2,4'-(1'-phenyl-1H-pyrazolin-5'-ones) and 4-(2-aminobenzyl)-1-phenyl-2-pyrazolin-5-ones; the proportion of each depended on the solvent system used. Reduction of the 4-(2-nitrobenzylidene)pyrazolones with sodium borohydride yielded the corresponding nitrobenzyl derivatives. These were reduced further with several reducing systems giving different compounds including spiro(indoline)pyrazolones and pyrazoloquinoline derivatives.

A study of the chemical reactivity of the isolated spiro-(N-hydroxyindoline)pyrazolones was undertaken. This included their reduction to the corresponding indolines, oxidation to 2-H-indolenine 1-oxide and reactions with nucleophilic reagents, in acid media, to form 5-substituted indoline derivatives. Acetylation and methylation gave N-acetyloxy and N-methyloxy derivatives and, in addition, some rearrangement products. Other rearrangements also occurred when attempts were made to benzoylate and sulfonate one of these spiro-N-hydroxyindolines.

Catalytic hydrogenation of the 4-(2-nitrobenzyl)pyrazolones in several solvents gave different and unexpected products which were found to be spiro(tetrahydroquinoline)pyrazolone derivatives. The solvent was involved in their formation, for which a mechanism is suggested. Eighteen of these compounds were also prepared by condensation of 4-(2-aminobenzyl)-1-phenyl-2-pyrazolin-5-ones with appropriate aldehydes.

A reinvestigation of the nature of the products obtained by sodium borohydride and palladium-charcoal reduction of two 4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-ones has revealed that, contrary to literature reports, none of the products is a cyclic hydroxylamine. Instead, the products were found to be thiols which readily oxidized in air to spiro(benzothiazoline)pyrazolones. Attempts to isolate N-hydroxy compounds by the reduction of the 4-(2-nitrophenylthio)pyrazolones using different reducing systems failed.

Catalytic hydrogenation of the 4-(2-nitrophenylthio)-pyrazolones did not produce spiro(dihydrobenzothiazine)pyrazolone derivatives. However, the latter compounds were readily obtained by the action of aldehydes on 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-ones.

The mass spectra of 1-hydroxy-2-phenyl-1,2-dihydropyridine and its O-benzoyl derivative as well as the mass spectra of three spiro(N-hydroxyindoline)pyrazolones, two O-acetyl derivatives and one O-methyl compound were recorded and interpreted. The N-hydroxy compounds demonstrated expulsions of $\dot{O}H$ radicals from the molecular ions. The loss of oxygen atoms and water molecules also occurred. The O-methyl compound showed an appreciable

expulsion of an OCH_3 radical from its molecular ion; $(M-59)^+$ and $(M-60)^+$ in the O-acetyl derivatives are due presumably to direct losses of a CH_3COO radical and a CH_3COOH molecule from the molecular ions.

Also, the mass spectra of six spiro(indoline)pyrazolones and two spiro(benzothiazoline)pyrazolones are discussed in detail. Their proposed fragmentations are substantiated by means of deuterium labelling and accurate mass measurements. All these compounds gave abundant molecular ions which fragmented mainly by the expulsions of CO and PhNCO molecules. Decomposition of the (M-CO) ions gave rise to many of the prominent fragments in the spectra.

In addition to the above compounds, the mass spectra of four simple pyrazolones, including the medicinal compounds antipyrine and aminopyrine, were recorded and interpreted. All these spectra contained several ions resulting from initial N-N bond cleavages; such a fragmentation has not been reported to occur in the pyrazolone nucleus. Strong ions at m/e 56 were found in the spectra of antipyrine and aminopyrine and also in some other 2,3-dimethyl pyrazolone derivatives prepared in this study; this ion could be of diagnostic value.

Some selected examples of the compounds prepared in this study, including two of the spiro(N-hydroxyindoline)pyrazolones were evaluated for neuroleptic and analgesic activity. The N-hydroxyindolines had only very weak sedative properties (p.o. or i.p.) and no analgesic activity (p.o.) at dose levels examined. The corresponding spiro(indoline) pyrazolones showed some neuroleptic and analgesic properties while 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one showed mild hypnotic effects.

ACKNOWLEDGEMENTS

It is with great pleasure that I cordially record my indebtedness and gratitude to my supervisor, Dr. R. T. Coutts, who guided this research since its inception, carefully read the manuscript, and contributed valuable criticisms and suggestions, all being inspired by the subtle mixture of his exceptional scholarship and good humor.

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My indebtedness to my home country, the Arab Republic of Egypt, and to its people, is beyond any verbal recognition. I am grateful to the University of Assiut for having allowed me a study leave and to the University of Alberta and to the Medical Research Council of Canada for their financial support.

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PREAMBLE

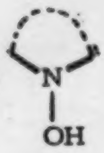
The ultimate aim of the proposed research was the synthesis of novel cyclic hydroxylamines, a study of their chemical reactions and a preliminary investigation of their pharmacological properties. Information on cyclic hydroxylamines is scattered throughout the scientific literature but the topic has not been reviewed. Consequently, it was considered necessary to compile a detailed review of the pertinent literature on these compounds and the introduction which follows is devoted entirely to this purpose.

During the course of the research described in this thesis, compounds other than cyclic hydroxylamines were also prepared and characterized. Relevant literature information on these compounds is included in the discussion section of the thesis.

CYCLIC HYDROXYLAMINES

1. INTRODUCTION

The structure of cyclic hydroxylamines (which will be also referred to as cyclic N-hydroxy compounds) may be represented as in (1). These compounds are disubstituted hydroxylamines (2) in which the N-hydroxy function is incorporated within a cyclic system.



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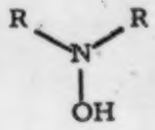

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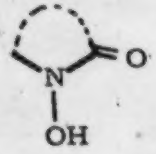

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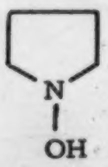
Although cyclic hydroxamic acids (3) are also cyclic N-hydroxy compounds, no attempt will be made to include them in the following discussion since they have recently been reviewed by several workers (Coutts, 1967; Bapat *et al*, 1969).

Simple examples of cyclic hydroxylamines are N-hydroxypyrrolidine (4), N-hydroxypyrazoles (5) and N-hydroxyisoxazolidine (6) to which reference will be made later in this introduction. In certain instances, cyclic N-hydroxy compounds exist in tautomeric equilibrium with a corresponding N-oxide (e.g. 7a $\leftrightarrows$ 7b), and the presence of one or both of these tautomers is dependent on the overall nature of the molecule. Some aspects of this tautomerism



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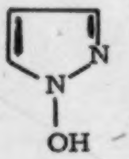

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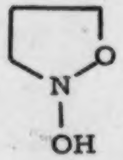

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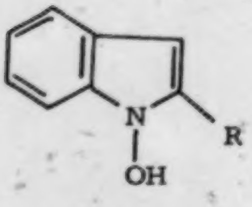

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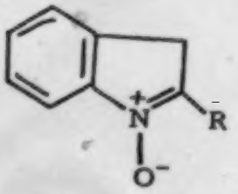

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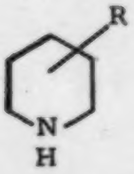
will be discussed in detail later.

Until the beginning of the last decade, very little attention was paid to the chemistry and biochemistry of hydroxylamines. Recent studies have been generally confined to aromatic hydroxylamines especially those found to be metabolites of carcinogenic amines. A comprehensive review of the chemistry of aliphatic and aromatic hydroxylamines, which also included some cyclic hydroxylamines, was recently published by German authors (Zeeh and Metzger, 1971). Also, Weisburger and Weisburger (1973) briefly summarized the chemistry of these compounds in their discussion which dealt mainly with the biochemical formation as well as pharmacological and toxicological properties of hydroxylamines and hydroxamic acids.

Some reasons for studying the chemical and biological properties of cyclic hydroxylamines are now suggested:

(a) More knowledge of the chemistry of these compounds is required in order to help understand the recent flood of biochemical studies in this area. N-hydroxylation, especially of free and N-acyl aromatic amines, is now a well recognized metabolic pathway (Irving, 1970; Weisburger and Weisburger, 1973). Like other hydroxylated metabolites, N-hydroxy derivatives are subject to further metabolic conversions such as conjugation with glucuronic, sulfuric and perhaps phosphoric acid, and reduction. The N-hydroxy metabolites are often reactive and generally more toxic than their parent amines. *In vitro*, they can combine as such, or after further reactions, with essential life supporting molecular species. Current studies suggest that metabolic N-hydroxylation of certain aromatic amines produces potentially carcinogenic (Miller, 1970; Gutmann *et al*, 1969), mutagenic (Miller and Miller, 1971) and nephrotoxic (Calder *et al*, 1973) products.

Until recently, biochemical N-hydroxylation studies were mostly confined to aromatic amines especially those which demonstrated carcinogenic activity. Some aliphatic amines were also studied but relatively little success was achieved in demonstrating N-hydroxylation. Beckett and Al-Sarraj (1972), however, showed that certain aliphatic amines do yield hydroxylamines, metabolically. So do secondary amines in which the nitrogen atom is a part of the ring system. Compounds based on the piperidine (8), morpholine (9) and piperazine (10) structures were found to be metabolized *in vitro* to the corresponding hydroxylamines. One of these, phenmetrazine (11) has been shown to oxidize to N-hydroxyphenmetrazine (12) *in vivo* in various animals. It was also shown (Beckett and Al-Sarraj, 1972)



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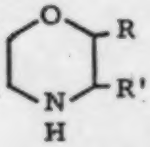

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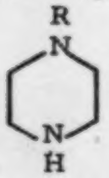

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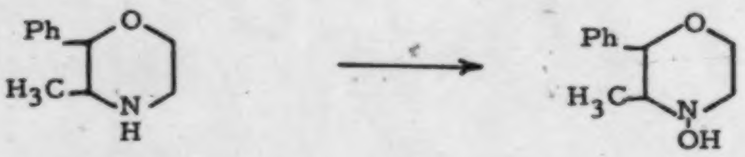
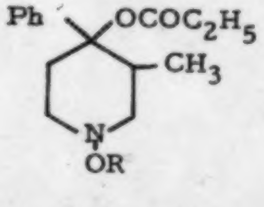


(11) (12)

that compounds structurally more complex than (8) also form hydroxylamines metabolically. For example, pipradol, normorphine, norcodeine and nortriptyline are metabolized to their corresponding hydroxylamines. It is not yet known, however, whether metabolic N-hydroxylation of all these compounds increases toxicity or whether it is sometimes a detoxification reaction.

(b) In addition to this flow of biochemical work, numerous reports on the pharmacological activity of cyclic N-hydroxy compounds have recently started to appear in the literature. Although studies in this area were limited and the early results were not outstanding (Johns and Major, 1927; Mamalis, 1971), recent studies describe diverse activities such as analgesic, adrenolytic, tranquilizing, muscle relaxant, anticonvulsant, antimicrobial and antiprotozoal properties for this type of compound.

Some α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines (13) were synthesized by Major and Dursch (1961) and examined for analgesic activity in rats. Two of these compounds (13, R=CH_3 or C_2H_5) showed strong oral activity but also many toxic manifestations. N-hydroxybenzodiazepine derivatives such as (14) have been screened for potential central nervous system (C.N.S.) depressant activity (Grindstedvaerket, 1967). Some related N-hydroxybenzodiazepines were also evaluated as anticonvulsants (Hoffman-LaRoche, 1966).



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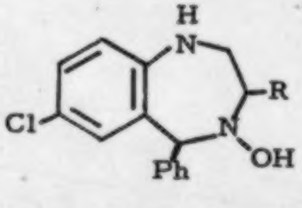

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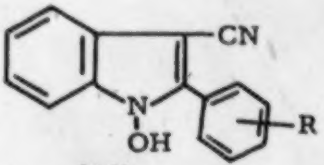
The N-hydroxyindole derivatives (15) were found to possess C.N.S. depressant as well as adrenolytic activity (Petracek, 1967). N-alkyloxybenzimidazole derivatives (16) also showed C.N.S. depressant, muscle relaxant and tranquilizing properties (Ciba, 1966; DeStevens *et al*, 1967). A variety of related compounds such as



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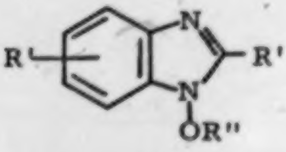
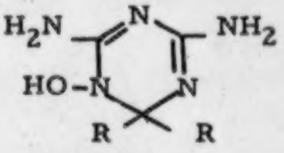


(16)

O-ethers of 1-hydroxyindoles and 1-hydroxybenzimidazole 3-oxides were found to be generally less active than (16) (DeStevens *et al*, 1967).

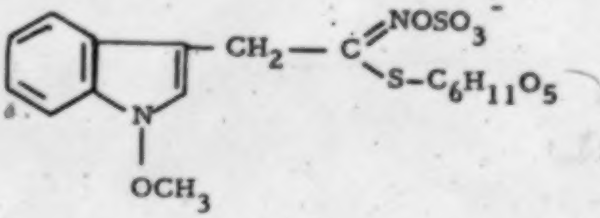
The antimicrobial properties of some O-ethers of 4,6-diamino-1,2-dihydro-1-hydroxy-1,3,5-triazines (17) were described by Mamalis *et al* (1965). These compounds were found to be active *in vitro* against a wide range of bacteria. Later investigations showed that these ethers possessed unexpected antimalarial properties



(17)

even against resistant strains of *Plasmodium berghei*. A related *bis*-triazine ether also showed trypanocidal activity of a high order in mice (Mamalis, 1971).

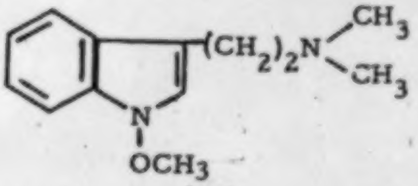
(c) The recent isolation of some derivatives of cyclic hydroxylamines from some plant and animal species demonstrated that these compounds exist in nature and stimulated further chemical and biological interest in cyclic hydroxylamines. All compounds isolated are derivatives of indole. A glucoside (18) which was named neoglucobrassicin was isolated from *Brassica napus* L. var. napobrassica (Gmelin and



(18)

Virtanen, 1962). This glucoside was identified on the basis of products formed from enzyme cleavage, acid hydrolysis and hydrogenolysis with Raney nickel.

Subsequently, a tryptamine alkaloid, 1-methoxy-3-(2-dimethylaminoethyl)indole (19) which was given the name lespedamine was isolated from the leaves of *Lespedeza bicolor* var. *japonica* (Morimoto and Oshio, 1965). A related N-methoxyindole derivative



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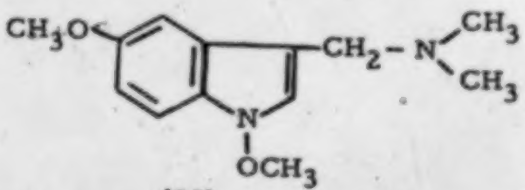
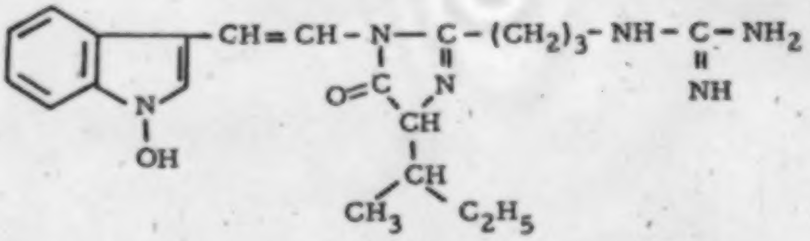


(20)

identified as 1,5-dimethoxy-3-dimethylaminomethyl)indole (20) was found to be the major alkaloid in *Gymnacranthera paniculata* var. zippeliana, (Johns *et al*, 1967). Both (19) and (20) were identified by their spectra and by their ease of reduction to the corresponding amines (NH for N-OCH$_3$).

In addition to these plant products, chemical studies on luciferin, a crystalline substance isolated from the firefly, *Cypridina hilgendorfii*, indicated that it was an N-hydroxyindole derivative (21)

(Hirata et al, 1959; Shimomura, 1960).



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2. PREPARATION OF CYCLIC HYDROXYLAMINES

Cyclic hydroxylamines have been prepared by various methods from a variety of precursors. These methods are conveniently grouped together for discussion in the following sections:

A) Preparation of cyclic hydroxylamines by direct N-oxidation of the corresponding amines.

B) Reduction of cyclic nitrones

C) Addition to cyclic nitrones

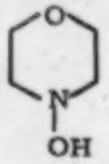
D) Formation of cyclic hydroxylamines by reductive or non-reductive cyclization reactions.

E) Miscellaneous preparations.

(A) Direct N-Oxidation of Secondary Cyclic Amines:

Reactions of this type are rarely used for the preparation of cyclic hydroxylamines, possibly due to the expected side reactions which might accompany the N-oxidation process. However, this method can be useful for the preparation of certain N-hydroxy compounds which might be difficult to obtain by other synthetic routes.

In most of these reactions hydrogen peroxide is employed with or without a catalyst as the oxidizing agent. 1-Hydroxymorpholine (22) was obtained by the oxidation of morpholine with different concentrations of hydrogen peroxide but the yields were generally poor (Henry and Dehn, 1950; Blout *et al*, 1958; Zinner and Kliegel, 1966). 1-Hydroxypiperidine (23) and 1-hydroxypyrrolidine (4) were similarly prepared (Blout *et al*, 1958). An attempt (Thesing and Sirrenberg, 1959) to improve the yield of these compounds by catalysing the reaction with methyl formate was unsuccessful but formic acid (Ruppert, 1960) and silicotungestic acid (Kawaguchi *et al*, 1967) were successfully used for this purpose.



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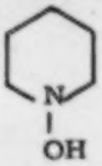

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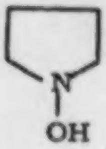
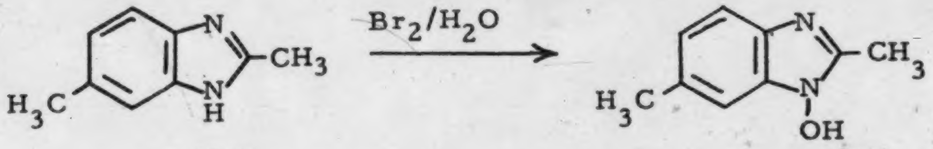


(4)

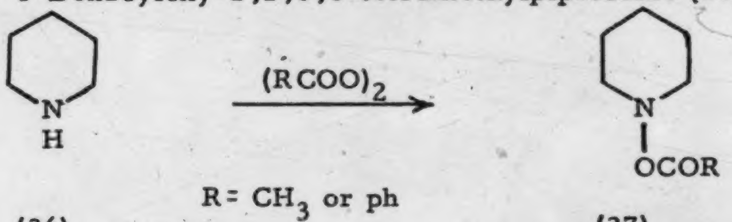
An early report (Ingraffia, 1933) that indole-magnesium bromide reacted with hydrogen peroxide to give 1-hydroxyindole was recently discounted by Kawana *et al* (1965). These investigators and others (e.g. Habib and Rees, 1962) failed to oxidize some cyclic amines to the corresponding hydroxylamines by means of hydrogen peroxide. Similarly, no cyclic N-hydroxy compounds were formed when ferric chloride was used (Dobeneck and Lehmerer, 1957; Kawana *et al*, 1965) although Houff *et al* (1954) reported earlier the oxidation of indole-3-acetic acid to the corresponding N-hydroxyindole using this reagent.

The use of percarboxylic acids for the N-oxidation of tertiary amines is very common and a considerable number of N-oxides have been prepared by this method. Recently, Beckett and Salami (1972) claimed that one of these acids (*m*-chloroperbenzoic acid) successfully oxidized phenmetrazine (11) to 1-hydroxyphenmetrazine (12). An earlier attempt (Stacy et al, 1964) to use percarboxylic acids for the preparation of 1-hydroxy-2-phenylbenzimidazole from the corresponding amine failed. The related compound, 2,6-dimethylbenzimidazole (24) was said to be oxidized by bromine to the corresponding hydroxylamine (25) (Niementowski, 1892).



(24) (25)

N-Acetoxy and N-benzoyloxypiperidines (27) can be prepared from piperidine (26) by the action of acetyl and benzoyl peroxides respectively (Gambarian, 1925; Gambarian and Kazaryan, 1933). 1-Benzoyloxy-2,2,6,6-tetramethylpiperidine (28) and 1-benzoyloxy-2,2,5,5-tetramethylpyrrolidine (29) were similarly prepared. Hydrolysis of (28) and (29) gave rise to the corresponding N-hydroxy compounds (Feldman and Hoffmann, 1964).



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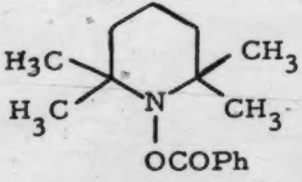

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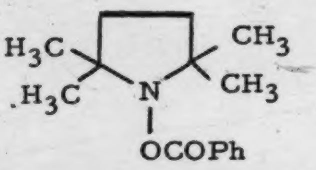
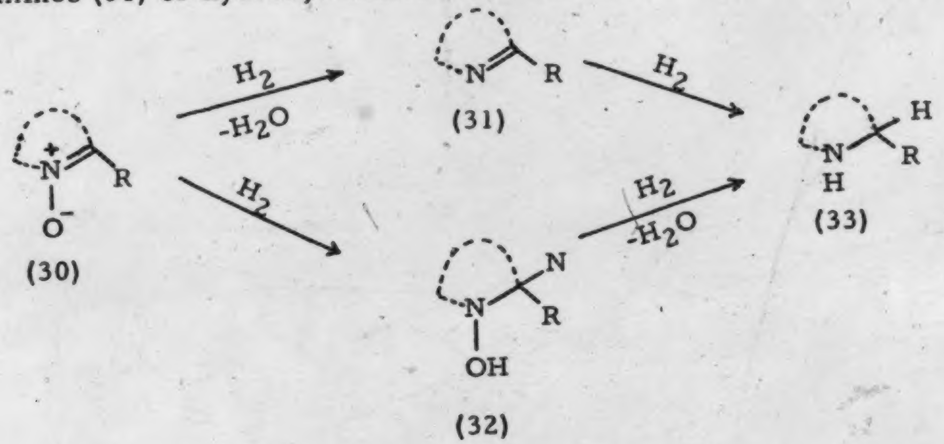


(29)

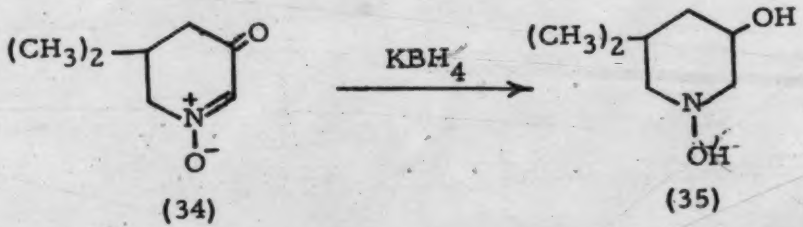
(B) Reduction of Cyclic Nitrones

Reduction of nitrones (30) to the corresponding secondary amines (33) can proceed by two different pathways. The intermediate imines (31) or hydroxylamines (32) have been isolated. Deoxygenation



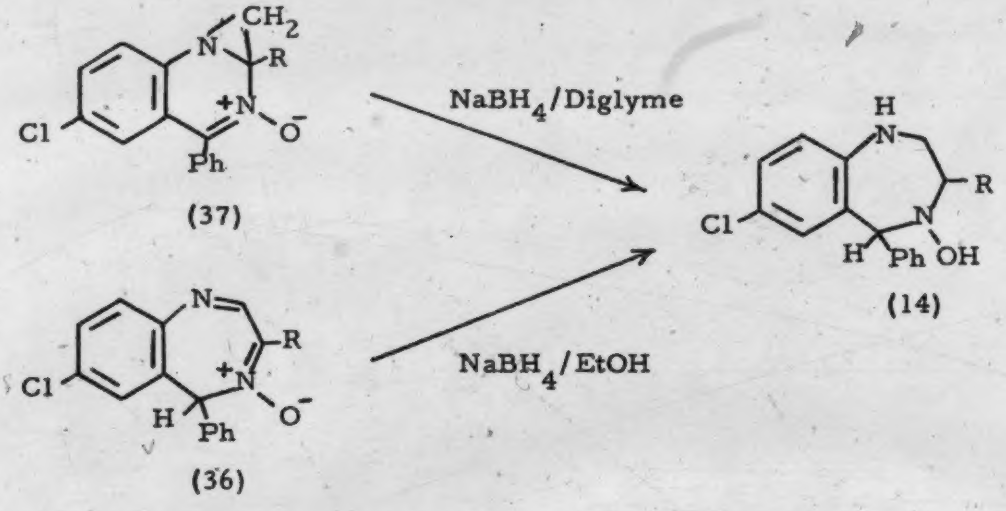
to (31) is generally effected by using triphenylphosphine, phosphorous trichloride, phosphorous oxychlorides, sulfur dioxide, zinc and acetic acid as well as catalytic hydrogenation. Zinc and mineral acids reduce the nitrone group to the secondary amine stage (33). Reductions with complex metal hydrides lead, in most cases, to the formation of hydroxylamines.

1,5-Dihydroxy-3,3-dimethylpiperidine (35) was prepared by the reduction of (34) using potassium borohydride (Brown *et al*, 1959).



The same reagent was used for the reduction of Δ'-pyrroline 1-oxides to the corresponding 1-hydroxypyrrolidines (Bonnett *et al*, 1959).

The N-hydroxybenzodiazepine (14, R=H) was prepared by reducing nitrones (36) or (37) with sodium borohydride in ethanol or diglyme. Reduction of the latter was accompanied by cleavage of the aziridine ring (Field *et al*, 1966). These reactions were also effected by using tetramethylammonium borohydride (Hoffmann-



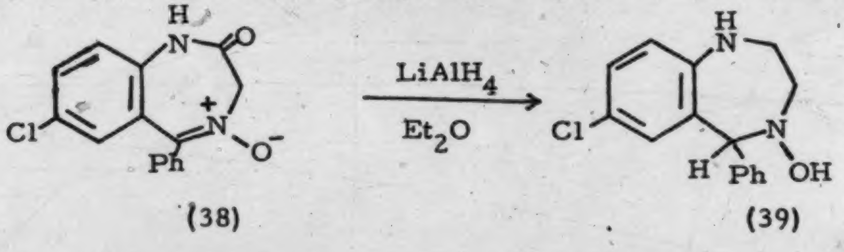
(37)

(36)

(14)

LaRoche, 1966).

The use of lithium aluminum hydride for the reduction of cyclic nitrones to the corresponding hydroxylamines was first reported by Exner (1955). There have been claims that reduction stops at the hydroxylamino- stage even when excess reagents and fairly vigorous conditions are used (Thesing and Sirrenberg, 1959). Among N-hydroxy compounds prepared in this way are 1-hydroxypyrrolidine from Δ'-pyrroline 1-oxide (Thesing and Sirrenberg, 1959) and 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (39) from the nitrone (38) (Sulkowski and Childress, 1963). 7-Chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine

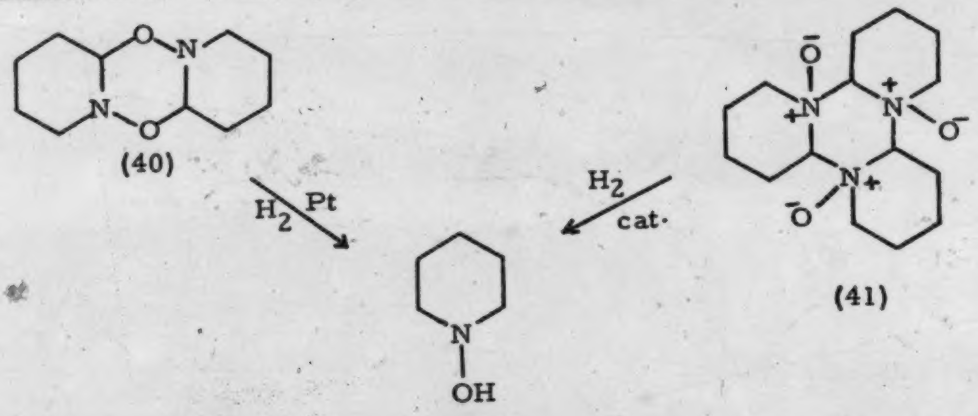


(38)

(39)

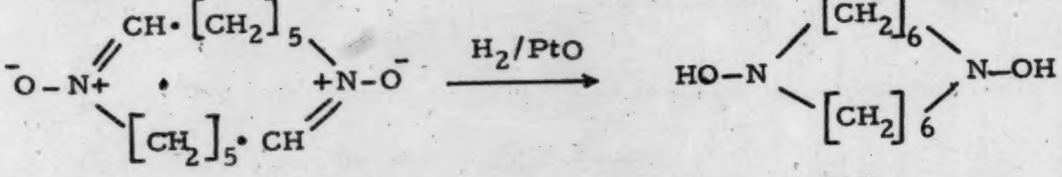
was prepared similarly (Sternbach and Reeder, 1961).

The dimeric 1,2,3,4-tetrahydropyridine 1-oxide (40) did not react with lithium aluminum hydride. However, it could be reduced catalytically over platinum in acidic methanol to give 1-hydroxypiperidine (23) (Thesing and Mayer, 1956). Catalytic hydrogenation of the trimer (41) afforded the same N-hydroxy compound



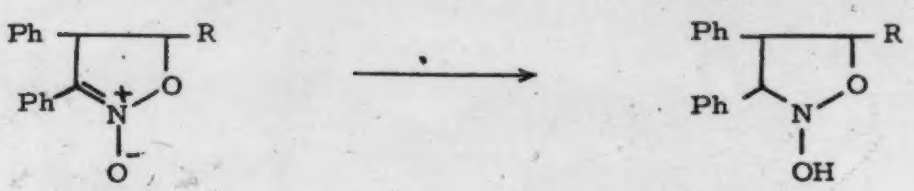
(40) (41) (23)

(Thesing and Mayer, 1957). The dimeric nitrone (42) was also hydrogenated in the presence of Adam's catalyst to give 1,8-dihydroxy-1,8-diazacyclotetradecane (43). Further hydrogenation of (43) over Raney nickel yielded the corresponding amines (Alford et al, 1966; Rogers, 1956).



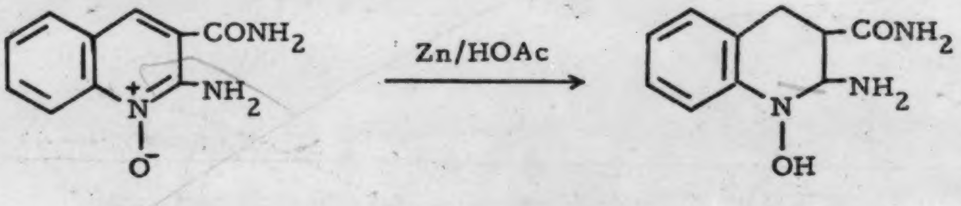
(42) (43)

More powerful chemical reagents are employed occasionally for the reduction of nitrones to hydroxylamines. The N-hydroxyisoxazoline (45) was formed when the isoxazoline 1-oxide (44) was reduced with zinc and acetic acid or with sodium iodide and acetic acid (Kohler and Barrett, 1926). The N-hydroxytetrahydroquinoline (47) was also prepared by the zinc and acetic acid reduction of (46) (Taylor and



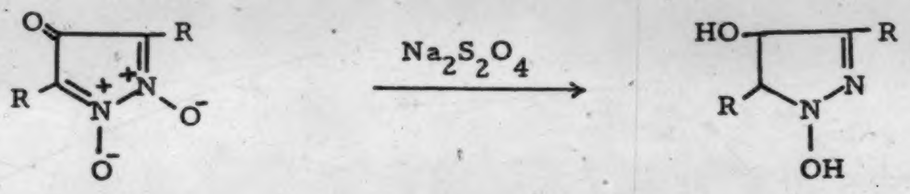
(44) (45)

and Kalenda, 1953). In contrast, the dioxide derivatives (48) were



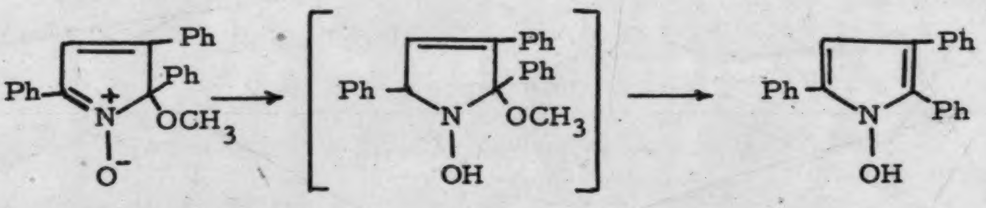
(46) (47)

reduced with sodium hydrosulfite to 1,4-dihydroxypyrazoles (49) but when reduction was performed with zinc and acetic acid, 4-hydroxypyrazoles (49, N-H for N-OH) were formed (Freeman et al, 1969).



(48) (49)

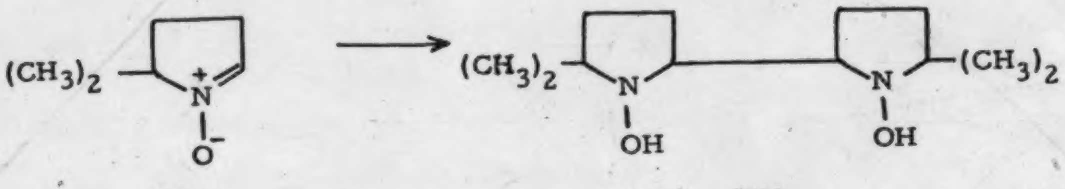
Reduction of the cyclic nitrone (50) was accompanied by an elimination of methyl alcohol and yielded the 1-hydroxypyrrole (51). This reduction was achieved using sodium-potassium alloy, alkyl or aryl magnesium bromides (Blatt, 1934). Sodium-potassium alloy was



(50) (51)

also reported to reductively dimerize 5,5-dimethyl-Δ'-pyrroline

1-oxide (52) to the 1,1'-dihydroxy-2,2'-bipyrrolidinyl derivative (53) (Clark et al, 1959).



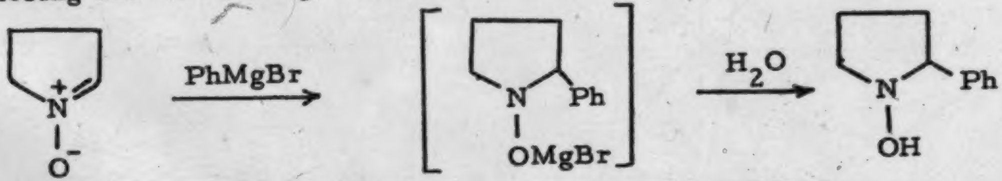
(52)

(53)

(C) Addition to Cyclic Nitrones:

Grignard reagents add across the double bond of cyclic nitrones leading, in certain instances, to the formation of stable cyclic hydroxylamines. Some α-alkyl and α-aryl N-hydroxy compounds were prepared in this way from pyrrolidine 1-oxides, piperidine 1-oxides, pyridine 1-oxides and quinoline 1-oxides.

1-Hydroxy-2-phenylpyrrolidine (55) was the product of the reaction of Δ'-pyrroline 1-oxide (54) and phenylmagnesium bromide (Thesing and Sirrenberg, 1959). Other N-hydroxypyrrolidines are prepared similarly (Bonnett et al, 1959; Delpierre and Lamchen, 1963).

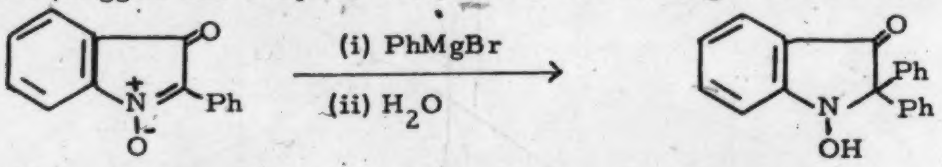


(54)

(55)

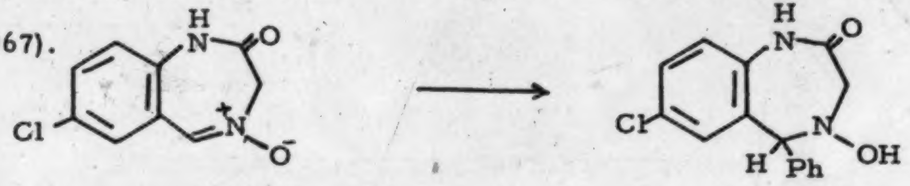
The tetrahydropyridine 1-oxide dimer (40), which is resistant to a number of nitrone reactions such as reduction with lithium aluminum hydride or with sulfur dioxide, reacted readily with phenylmagnesium bromide to give 1-hydroxy-2-phenylpiperidine (Thesing and Mayer, 1956, 1957).

2,2-Diphenyl-3-oxo-1-hydroxyindoline (57) was formed from the reaction of 2-phenylisatogen (56) and phenylmagnesium bromide (Rugguli and Casper, 1939). The latter reagent also reacted



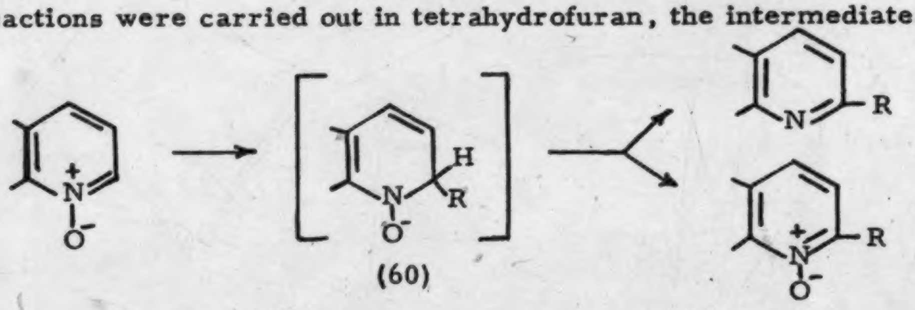
(56) (57)

with the cyclic N-oxide (58) to yield 7-chloro-4-hydroxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (59) (Grindstedvaerket, 1967).



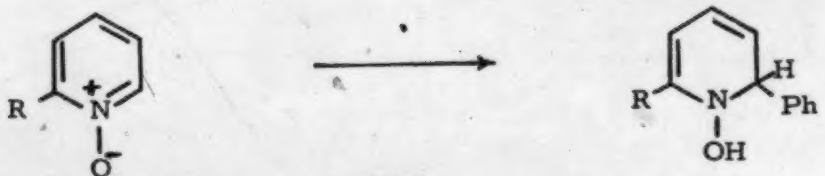
(58) (59)

Addition of Grignard reagents to pyridine 1-oxides and quinoline 1-oxide generally gives α-alkyl and α-arylpyridines quinolines (Colonna, 1936; Ochiai and Arima, 1950). In some instances, the intermediates (60) are also oxidized by the unreacted N-oxides in the reaction mixture to form α-substituted N-oxides (Colonna and Risaliti, 1954; Kato and Yamanaka, 1965). When these reactions were carried out in tetrahydrofuran, the intermediates (60)



(60)

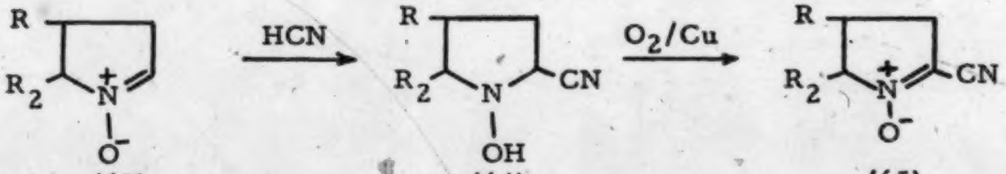
afforded cyclic N-hydroxy compounds. Thus, 1-hydroxy-2-phenyl-1,2-dihydropyridine (62a), its 6-methyl derivative (62b) and 1-hydroxy-2-phenyl-1,2-dihydroquinoline were obtained by the reaction of phenylmagnesium bromide with pyridine 1-oxide, 2-picoline 1-oxide and quinoline 1-oxide respectively. Attempts to repeat this reaction with



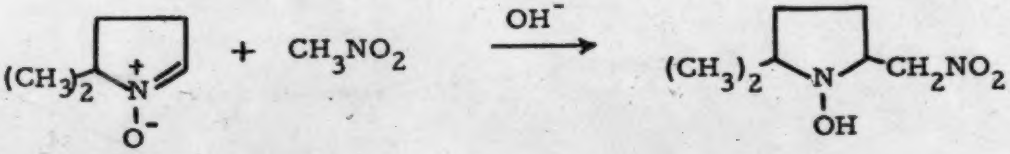
(61) a, $R=H$ b, $R=CH_3$ (62)

4-substituted quinoline 1-oxides failed to yield any N-hydroxy compounds (Kato and Yamanaka, 1965).

Hydrogen cyanide is reported to add across the double bond of nitrones giving adducts which generally lose water in the presence of bases. This reagent, however, reacted with the pyrroline 1-oxides (63) to give 2-cyano-1-hydroxypyrrolidines (64) which were stable to alkali but readily oxidized to the cyanonitrones (65) (Bonnett et al, 1959). Cyclic nitrones also react with active hydrogen compounds forming simple adducts. For example, treating pyrroline 1-oxides such as (52) with nitromethane, in the presence of base, yielded the 2-nitromethyl-1-hydroxypyrrolidine (66) (Bonnett et al, 1959; Bowering et al, 1963).

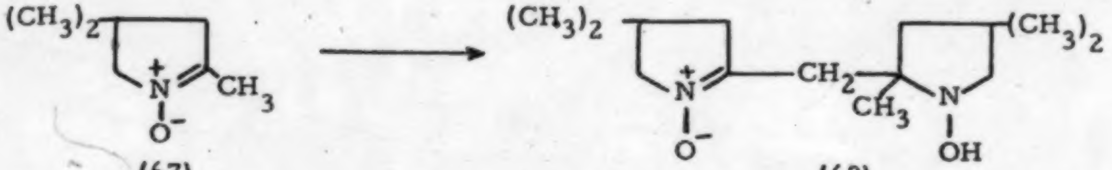


(63) (64) (65)



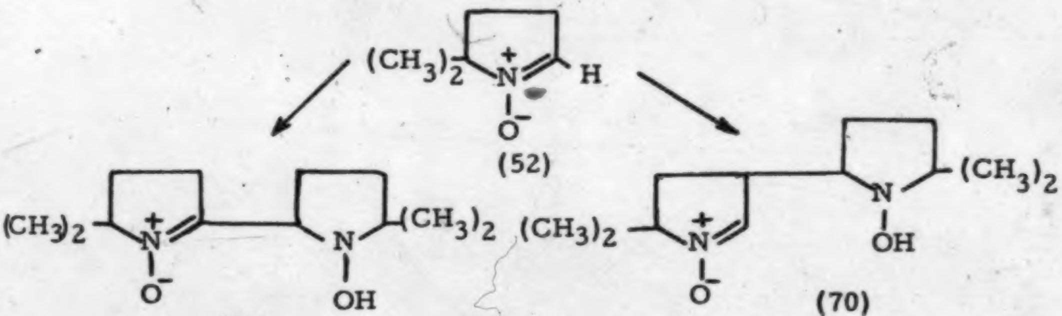
(52) (66)

Some nitrones undergo aldol-type reactions, 2,4,4-Trimethyl-Δ'-pyrroline 1-oxide (67), for example, dimerizes slowly on standing to give the nitrone-hydroxylamine (68) (Brown et al, 1959a).

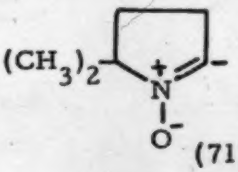


(67) (68)

Dimerization was also induced and controlled by basic catalysts. Thus, the nitrone (52) is stable at room temperature but readily dimerizes under basic conditions. In the presence of triphenylmethyl sodium, an aldol-type reaction occurred leading to the bipyrrolyl derivative (70) while a benzoin-type dimerization to (69) occurred with sodamide in liquid ammonia. Sodamide in triethylamine gave a mixture of both dimers (Brown et al, 1959b, 1959c). The benzoin-type



(69) (70)



(71)

dimerization might be initiated by deprotonation of (52) to form the anion (71) (Brown et al, 1965).

(D) Cyclization Reactions:

The majority of cyclic hydroxylamines reported in the literature were prepared by cyclization reactions which involve either condensation of two molecules or the intramolecular cyclization of a single compound. These reactions generally utilize nitro or oxime derivatives. Nitroso and hydroxylamino compounds are possible intermediates in many cases and are sometimes used as initial reagents. The mechanisms of these cyclization reactions are seldom clear and accordingly the discussion of these mechanisms is mostly speculative.

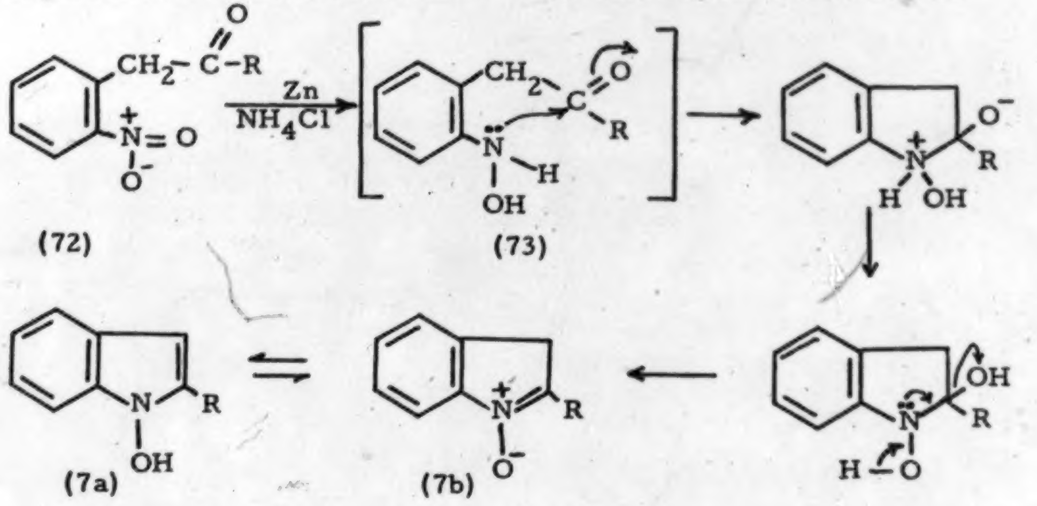
Most often, especially when nitro compounds or oximes are used, an initial reductive step is required prior to cyclization and numerous reducing systems have been employed for this purpose. However, the nitro group may also cyclize without initial reduction to the nitroso or hydroxylamino stages. This alternative route involves nucleophilic attack on the nitrogen atom of the nitro-group; the attacking nucleophile can be an aliphatic carbanion, a reactive aromatic ring or an amino group. These types of reactions were extensively reviewed by London and Tennant (1964).

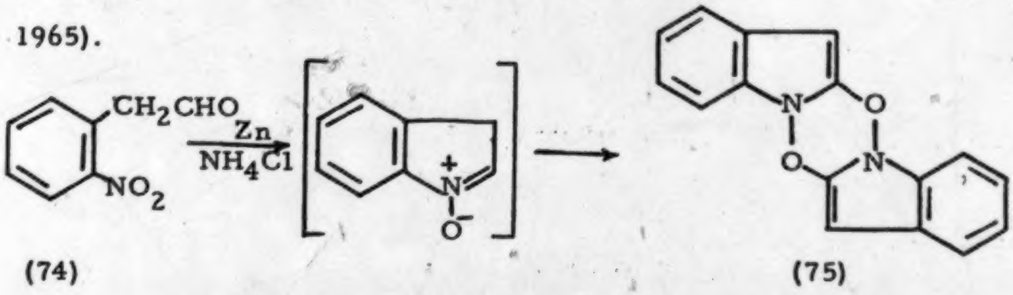
Cyclization reactions discussed now are classified under two subheadings, reductive and non-reductive cyclizations. In the first, a reducing agent is used, mainly to effect reduction of the oxime or nitro-group to a hydroxylamino or nitroso function. The second group includes those reactions in which the nitro-group's demand for electrons is supplied from within the molecule. Miscellaneous reactions in which cyclization involves quite different mechanisms will also be reviewed.

i - Reductive cyclizations:

Various reducing agents have been employed for the reductive cyclization of oximes and nitro compounds. These reducing agents are generally mild although, in some cases, strong reduction systems give rise to the required N-hydroxy compounds.

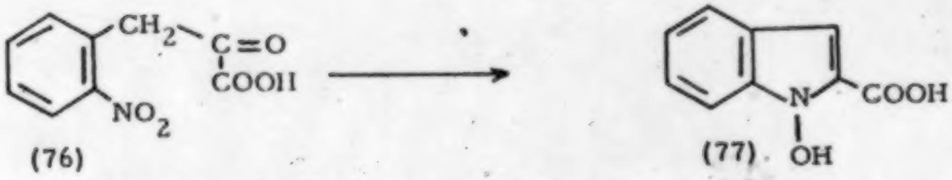
Zinc and ammonium chloride have been used by several investigators for the preparation of aromatic hydroxylamines from the corresponding nitro compounds. Reduction of o-nitrobenzyl ketones (72) with this system was also successful and resulted in the formation of the tautomeric 1-hydroxyindoles (7a ⇌ 7b). The hydroxylamine (73) was postulated as an intermediate. The same synthetic route was employed in an attempt to prepare the parent N-hydroxyindole, but it led instead to a dimer formulated as (75) (Mousseron-Canet and Boca, 1965).





Reduction of 2-nitrophenylpyruvic acid (76) with sodium-amalgam offered a means of preparing 1-hydroxyindole-2-carboxylic acid (77) (Reissart, 1897). Similar results were obtained when 4-methyl-2-nitrophenylpyruvic acid was reduced. Reduction of (76) with zinc and acetic acid yielded indole 2-carboxylic acid.

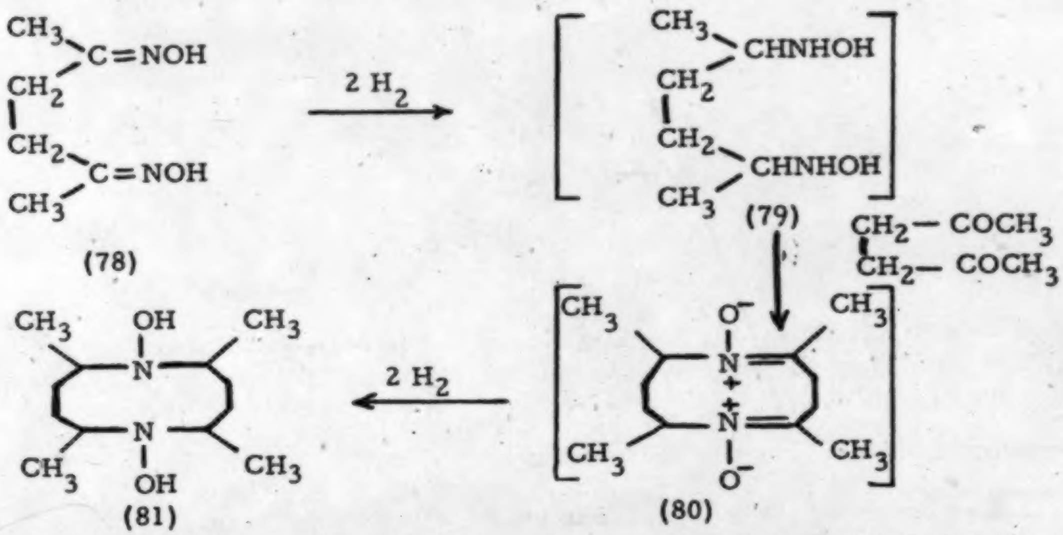
The same N-hydroxyindole (77) was the sole acidic product obtained by the sodium borohydride/palladium-charcoal



reduction of 2-nitrophenyl pyruvic acid (76) or its methyl ester; from the latter a better yield was obtained (Coutts and Wibberley, 1963).

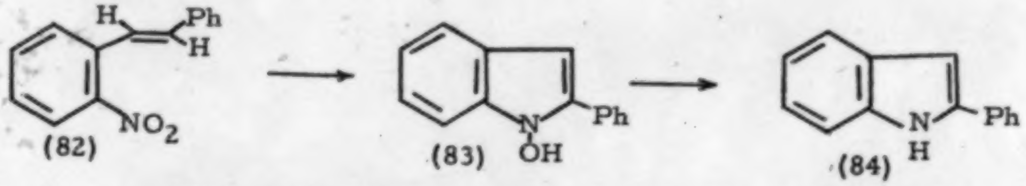
Catalytic hydrogenation of the oxime, semicarbazone and phenylhydrazone of 2-nitrophenylpyruvic acid (76) over platinum or palladium provided another route to 1-hydroxyindole-2-carboxylic acid (77) (Baxter and Swan, 1967). Varying amounts of indole-2-carboxylic acid were also formed along with the hydroxyindole.

Another example of the use of catalytic hydrogenation for preparing cyclic hydroxylamines was reported earlier by Krajcinoric and Vranjican (1933). Hydrogenation of acetyonylacetone dioxime (78) in acidic medium produced 1,6-dihydroxy-2,5,7,10-tetramethyl-1,6-diazacyclodecane (81). This compound was formed by the reduction of the intermediate dioxy derivative (80) which resulted from the condensation of the hydroxylamine (79) with acetonylacetone; the latter is present on account of the partial hydrolysis of the dioxime in acidic

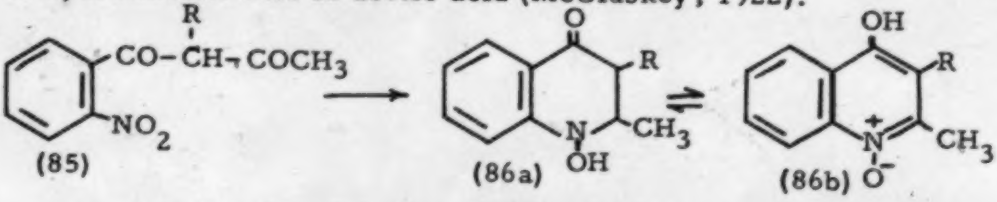


medium.

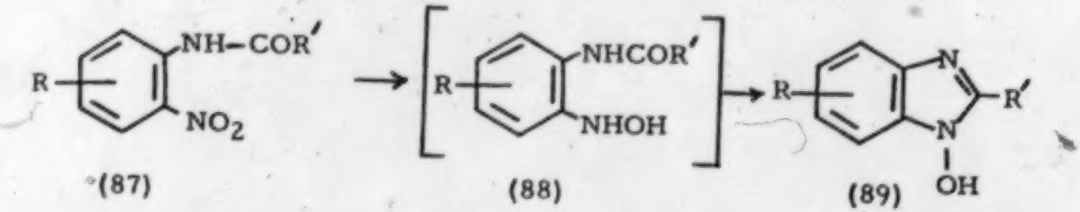
Reductive cyclization of trans-o-nitrostilbene (82) with triethylphosphite yielded 2-phenylindole (84) and traces of two other products. When this reaction was interrupted after one hour, the intermediate 1-hydroxy-2-phenylindole (83) was isolated, but only in poor yield (Sundberg, 1965).



The tautomeric N-hydroxyquinolone (86, R=H) was prepared by the stannous chloride/hydrogen iodide reduction of ethyl o-nitrobenzoylacetone (85, R=H) (Gabriel and Gerhard, 1921). The related compound (86, R=COOEt) was obtained by the reduction of ethyl o-nitrobenzoylacetoacetate (85, R=COOEt) with stannous chloride and hydrochloric acid in acetic acid (McCluskey, 1922).

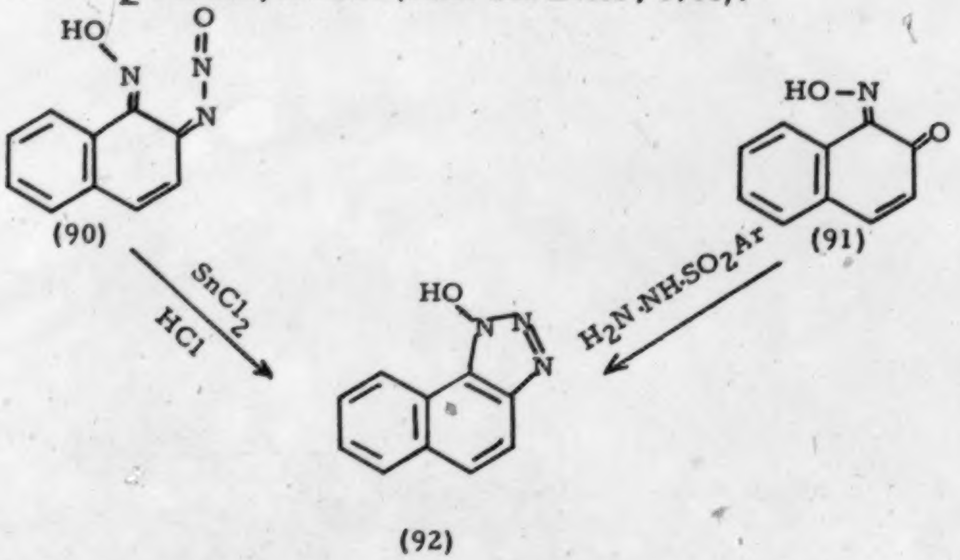


Reduction of o-nitroanilides (87) under mild conditions resulted in the formation of 1-hydroxybenzimidazoles (89). The hydroxylamine (88) was postulated as an intermediate. Among the reducing systems used in this type of reaction are zinc and ammonium chloride (Niementowski, 1910; Kuhn and Blau, 1958), zinc and hydrochloric acid (Niementowski, 1892, 1899), tin and hydrochloric acid (Baczynski and Niementowski, 1902); ammonium sulfide (Bankiewicz, 1889; Niementowski, 1910; Takahashi and Kano, 1964), sodium dithionite (Fries and Reity, 1937; De Stevens et al, 1967) and catalytic hydrogenation over palladium (Kamel et al, 1957).

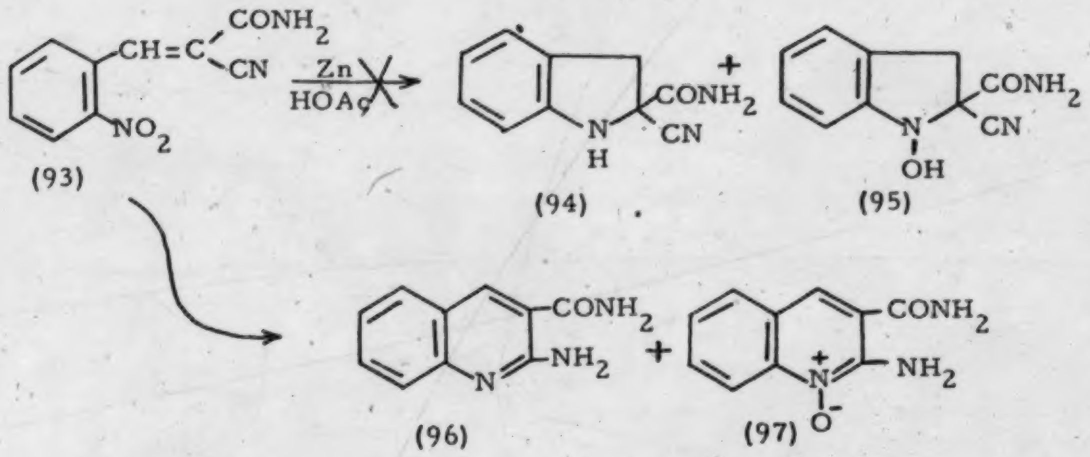


Ammonia (Neadle and Pollitt, 1967) as well as sodium hydroxide (De Stevens et al, 1967) were also used to catalyze this cyclization.

The 1-hydroxybenzotriazole derivative (92) has been prepared either by the stannous chloride/hydrochloric acid reduction of the potassium salt of the 2-nitrosoimino oxime (90) (Harden and Okell, 1901) or by the interaction of 1,2-naphthoquinone 1-oxime (91) and toluene p-sulfonhydrazide (Scott and Lelor, 1966).

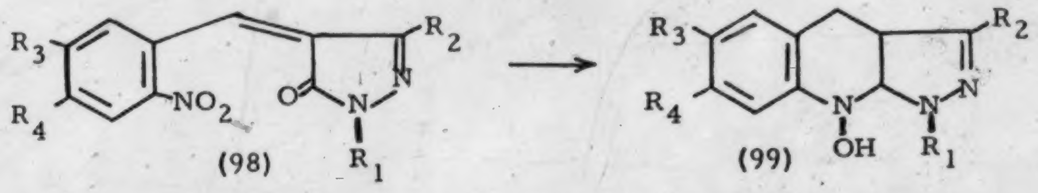


An early report (Heller and Wunderlich, 1914) that reduction of α-cyano-o-nitrocinnamide (93) by zinc and acetic acid yielded 2-carbonyl-2-cyanodihydroindole (94) and its N-hydroxy derivative (95) was later discounted. The products have been reformulated as 2-aminoquinoline-3-carboxamide (96) and its N-oxide (97)(Pachter and Kloetzel, 1951; Taylor and Kalenda, 1953;


CONH2
CH=C
CN
NO2
(93)
Zn
HOAc
CONH2
CN
N
H
(94)
+
CONH2
CN
N
OH
(95)
CONH2
NH2
N
(96)
+
CONH2
NH2
N
O
(97)

Tyler, 1955).

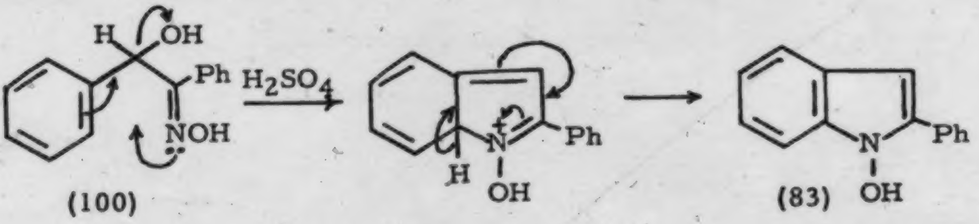
Another report by Narang et al (1934) and the related work by Coutts and Edwards (1966) regarding the formation of the N-hydroxypyrazoloquinolines (99) by the reduction of the o-nitrobenzylidene derivatives (98) constitutes a part of the present investigation and will be discussed in detail later.


R3
R4
NO2
O
N
N
R2
R1
(98)
R3
R4
N
OH
N
N
R2
R1
(99)

ii - Non-reductive cyclization:

In most cases, these cyclizations are catalyzed by acids or bases and the products occasionally are affected by the pH of the reaction media. Some interactions, however, occur under seemingly neutral conditions.

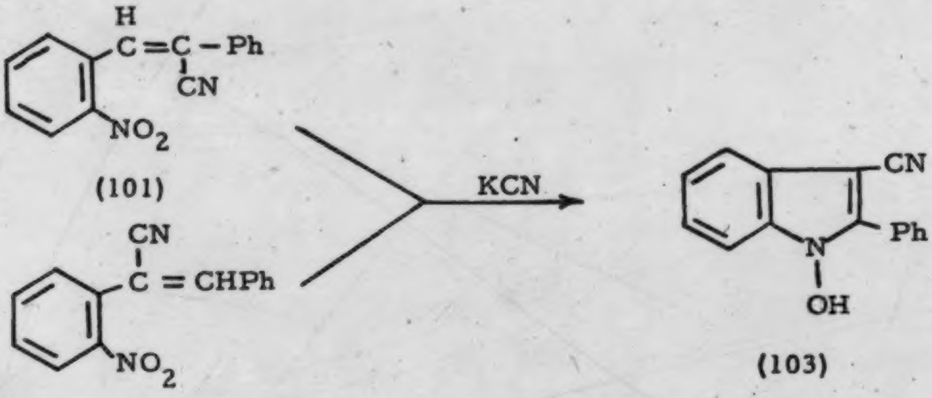
One of the earliest examples of acid-catalyzed cyclizations was that reported by Fischer and Hutz (1895). Treatment of the benzoin oxime (100) with concentrated sulfuric acid resulted in the formation of 1-hydroxy-2-phenylindole (83). A similar procedure was recently employed for the preparation of some related N-hydroxyindoles (Kawana *et al*, 1965).



(100)

(83)

The related 3-cyano-1-hydroxy-2-phenylindole (103) was obtained by the action of potassium cyanide on either *o* nitro-α-phenylcinnamonitrile (101) or α-*o*-nitrophenylcinnamonitrile (102). Alkaline hydrolysis and decarboxylation of (103) yielded 1-hydroxy-2-phenylindole (83) (Loudon and Tennant, 1960).

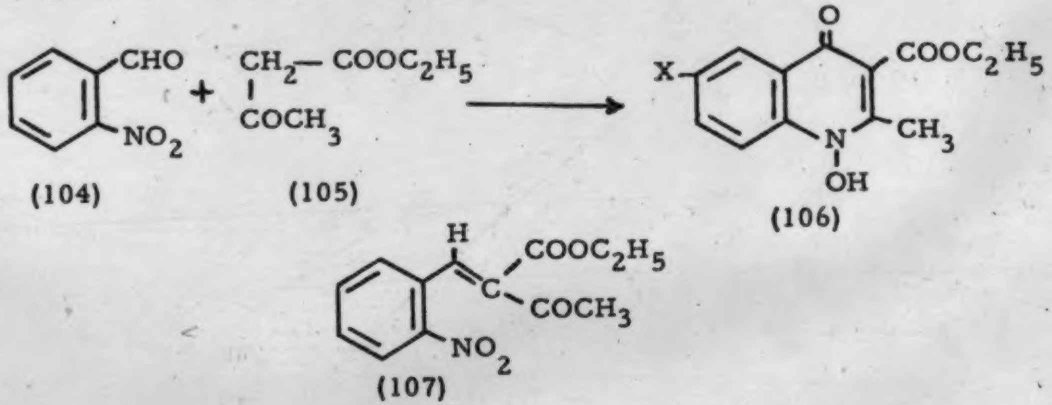


(101)

(102)

(103)

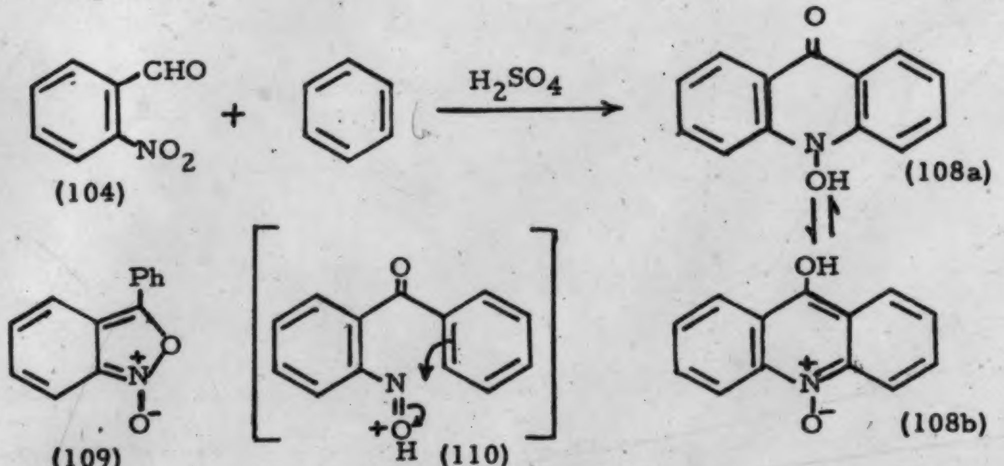
The acid-catalyzed condensation of *o*-nitrobenzaldehyde (104) with ethylacetoacetate (105) gave a 1-hydroxyquinolone derivative (106) (Loudon and Wellings, 1960). Analogous results were obtained by replacing the ketoester (105) with acetylacetone, benzoylacetone or diethylacetone dicarboxylate. When hydrogen chloride was used to catalyze the reaction, a chlorine atom was introduced into the product (106, X=Cl). However, no brominated derivatives were formed when hydrogen bromide was used. In the presence of quinol, the isolable intermediate (107) may be cyclized even by hydrogen chloride without any uptake of chlorine (Loudon and Tennant, 1962).


CHO
NO2
CH2— COOC2H5
COCH3
X
O
COOC2H5
CH3
N
OH
H
COOC2H5
C
COCH3
NO2

(104) (105) (106)

(107)

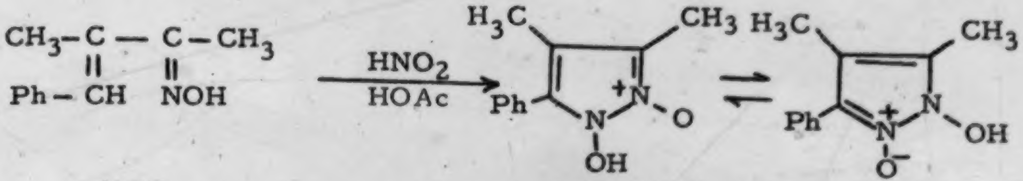
o-Nitrobenzaldehyde (104) reacted with benzene in the presence of sulfuric acid to give 10-hydroxyacridone (108) (Lehmstadt, 1932; Kliegl and Brosamle, 1936). The anthranil oxide (109) and the nitroso compound (110) were suggested as intermediates (Katritzky and Logowski, 1971).


CHO
NO2
H2SO4
O
N
OH
Ph
O
N
O
O
N
O
H
OH
N
O

(104) (108a)

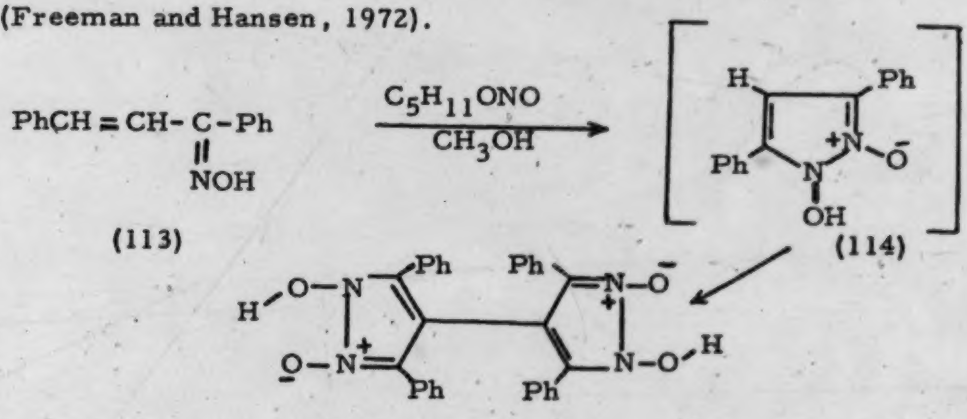
(109) (110) (108b)

Nitrosation of 3-methyl-4-phenyl-3-buten-2-one oxime (111) yielded a high melting product which was initially assigned a nitrimine structure (Harris and Tietz, 1904) but was subsequently shown by Freeman and Gannon (1966) to be the 1-hydroxypyrazole 2-oxide (112a) or its 2-hydroxy 1-oxide tautomer (112b). Further studies (Freeman and Gannon, 1969; Freeman et al, 1969) showed



(111) (112a) (112b)

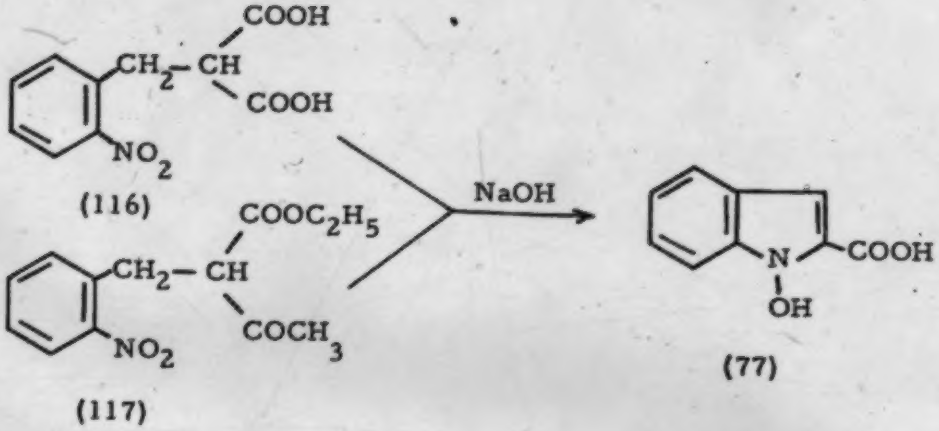
that the products obtained from this reaction are dependent on the substituents on the oxime molecule. An attempt to prepare the N-hydroxy N-oxide (114) by nitrosation of benzalacetophenone oxime (113) resulted instead in the formation of a dimeric product (115) (Freeman and Hansen, 1972).



(113) (114)

(115)

The ability to form cyclic N-hydroxy compounds by base-catalyzed cyclizations has been known for some time. Reissart (1896) found that treatment of o-nitrobenzylmalonic acid (116) with aqueous sodium hydroxide solution yielded 1-hydroxyindole-2-carboxylic acid (77). This compound was also obtained by the action of the same base on o-nitrobenzylacetoacetate (117) (Gabriel et al, 1923). The latter reaction occurred so readily that the ester (77, $COOC_2H_5$ for COOH) was also isolated.

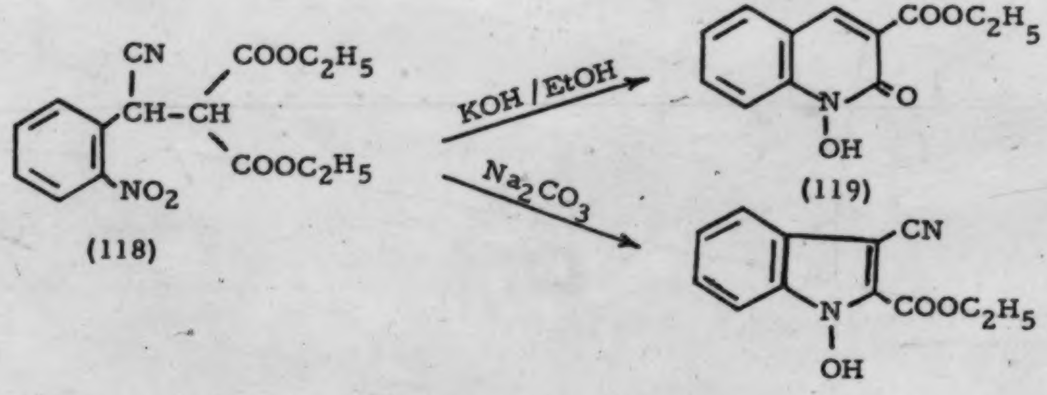

COOH
CH$_2$–CH
COOH
NO$_2$
COOC$_2$H$_5$
CH$_2$–CH
COCH$_3$
NO$_2$
NaOH
N
COOH
OH

(116)

(117)

(77)

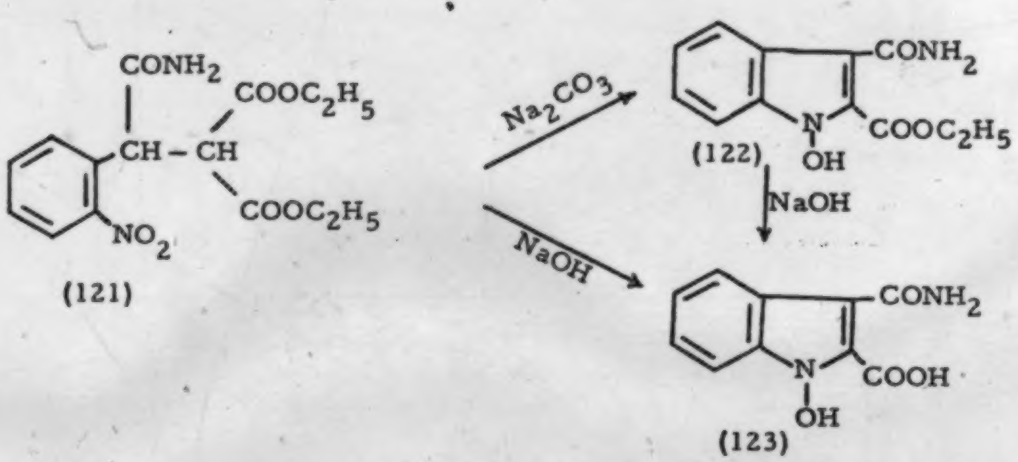
Base-catalyzed cyclizations of diethyl-α-cyano-α-2-nitrobenzylmalonate (118) and its α-carbamoyl analog (121) produced different products depending on the type of base used. Thus, treatment of (118) with ethanolic potassium hydroxide yielded the 1-hydroxyquinolone (119) while the use of aqueous sodium carbonate led to the formation of ethyl 3-cyano-1-hydroxyindole-2-carboxylate (120). On the other hand, treatment of the α-carbonylmalonate (121) with aqueous sodium hydroxide gave the acid amide (123) while the corresponding ester (122) was obtained when sodium carbonate was used (Loudon and Wellings, 1960). These cyclizations have been explained


CN
COOC$_2$H$_5$
CH–CH
COOC$_2$H$_5$
NO$_2$
KOH / EtOH
Na$_2$CO$_3$
COOC$_2$H$_5$
N
O
OH
CN
N
COOC$_2$H$_5$
OH

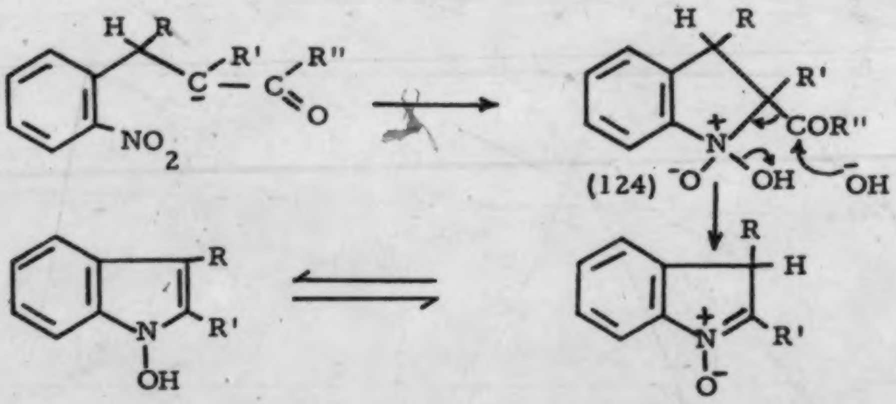
(118)

(119)

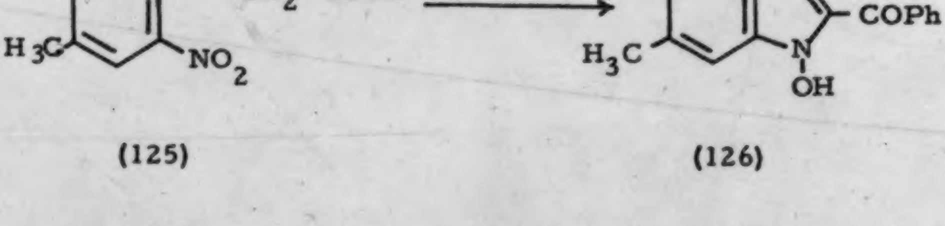
(120)


CONH$_2$
COOC$_2$H$_5$
CH – CH
COOC$_2$H$_5$
NO$_2$
(121)
Na$_2$CO$_3$
NaOH
CONH$_2$
COOC$_2$H$_5$
N
OH
(122)
NaOH
CONH$_2$
COOH
N
OH
(123)

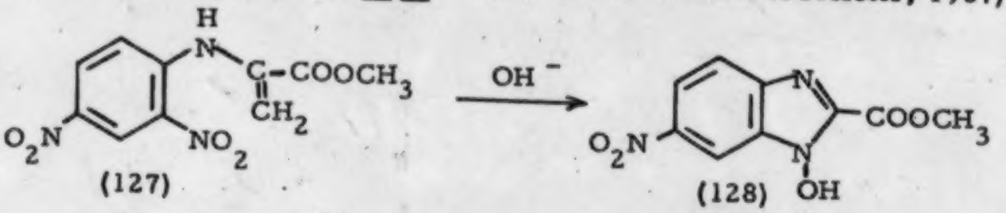
in terms of intramolecular condensation reactions of carbanions with the nitro groups followed by decomposition of the internal condensate (124) (Loudon and Wellings, 1960).


H
R
R'
R"
C
C
O
NO$_2$
H
R
R'
COR"
N
$^-$O
OH
$^-$OH
(124)
R
H
R'
N
O$^-$
R
R'
N
OH

2-Nitro-N-phenacyl-p-toluidine (125) was found to cyclize in the presence of ethanolic potassium hydroxide to the 1-hydroxyimidazole (126) (Loudon and Tennant, 1963). The analogous 1-hydroxy-

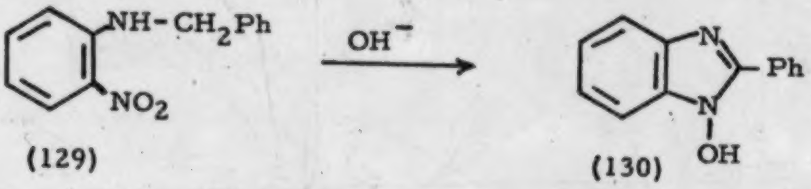

H
N
CH$_2$–COPh
H$_3$C
NO$_2$
KOH/EtOH
N
COPh
H$_3$C
N
OH
(125)
(126)

2-methoxycarbonyl-6-nitrobenzimidazole (128) was obtained by the base-catalyzed cyclization of methyl α-(2,4-dinitrophenylamino)-acrylate (127) (Luetzov et al, 1966; Luetzov and Vercellotti, 1967).



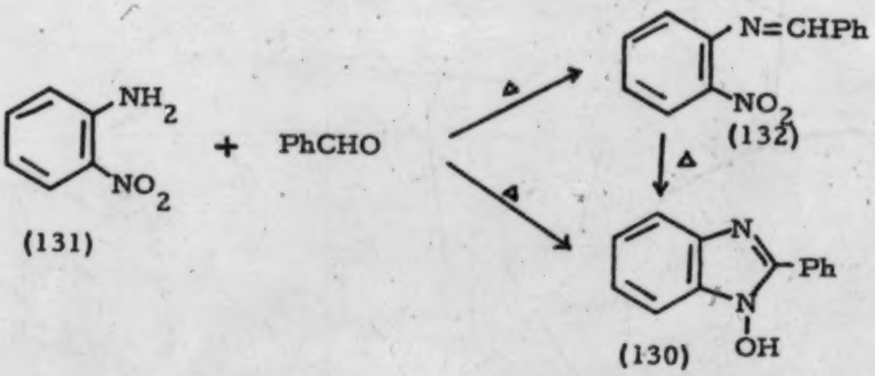
(127) (128)

1-Hydroxy-2-phenylbenzimidazole (130) was prepared by the base-catalyzed cyclization of N-benzyl-o-nitroaniline (129) (Stacy et al, 1966). The same compound was also obtained by the reaction of



(129) (130)

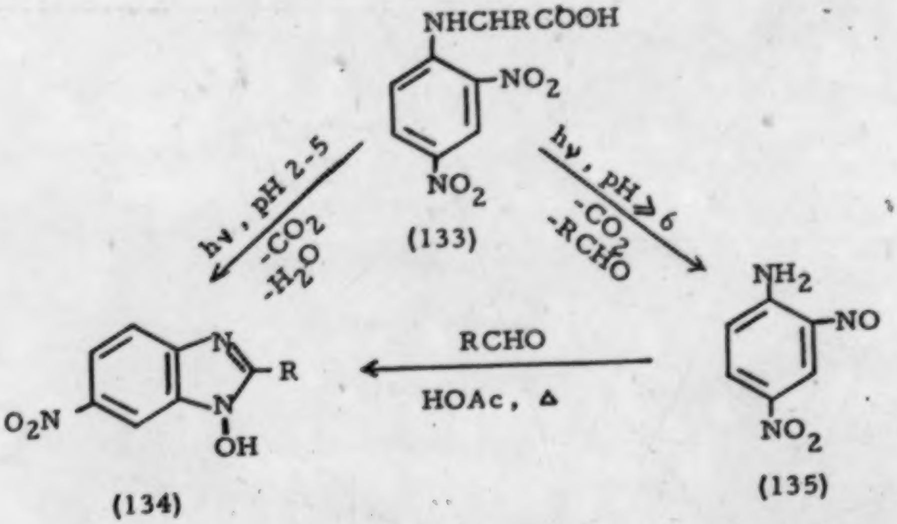
benzaldehyde and o-nitroaniline (131) and by the prolonged heating of the isolable intermediate benzal-o-nitroaniline (132) (Stacy et al, 1964).



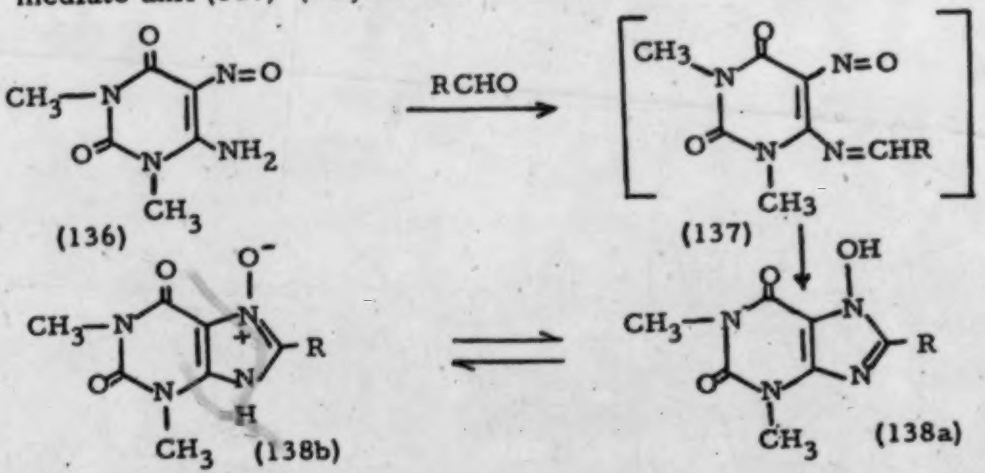
(131) (132) (130)

The analogous 1-hydroxybenzimidazole derivative (134) were prepared by the photolytic conversion of 2,4-dinitrophenyl derivative of α-amino-acids (133). This reaction also produced 4-nitro-2-nitrosoaniline (135). The proportion of these two products depends on the pH of the solution (Pollitt, 1965; Neadle and Pollitt, 1967). Reaction of (135) with different aldehydes yields 1-hydroxy-6-

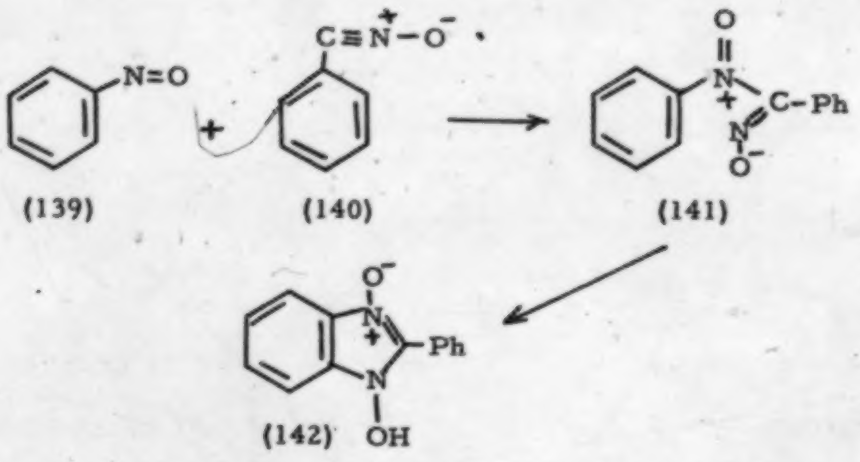
nitrobenzimidazoles (134) (Russel, 1965).


NHCHRCOOH
NO_2
NO_2
(133)
hν, pH 2-5
$-CO_2$
$-H_2O$
hν, pH ≥ 6
$-CO_2$
-RCHO
NH_2
NO
NO_2
(135)
RCHO
HOAc, Δ
O_2N
R
N
N
OH
(134)

Treatment of 1,3-dimethyl-4-amino-5-nitrosouracil (136) with benzaldehyde and dimethylformamide yielded the tautomeric N-hydroxypurine (138) as one of the reaction products. This compound is probably formed by the spontaneous cyclization of the intermediate anil (137) (Taylor and Garcia, 1964).

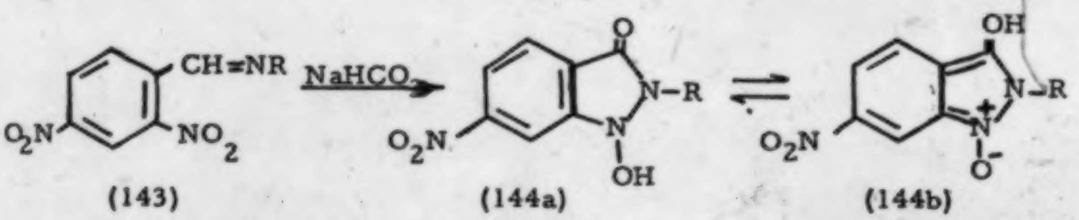

O
N=O
CH_3
N
O
N
NH_2
CH_3
(136)
RCHO
CH_3
N=O
N=CHR
CH_3
(137)
O^-
CH_3
R
+
H
CH_3
(138b)
OH
CH_3
R
CH_3
(138a)

1-Hydroxy-2-phenylbenzimidazole 3-oxide (142) was obtained by the interaction of nitrosobenzene (139) with benzonitrile oxide (140). The intermediate (141) has been isolated at low temperature (Minisci *et al*, 1963). Related compounds have also been prepared


(139) (140) (141) (142)

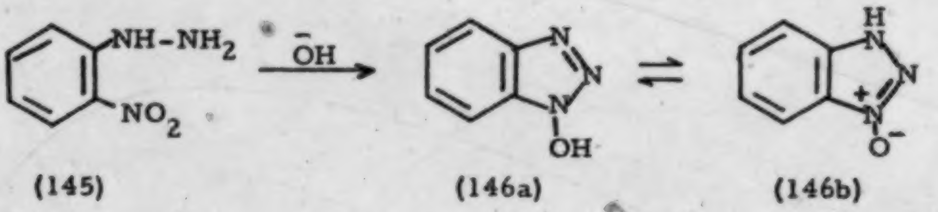
by the reaction of o-quinone dioxime with aldehydes (Boulton et al, 1966, 1967).

The 1-hydroxyindazolone derivatives (144a) which are tautomeric with 3-hydroxy-indazole-1-oxide (144b) were reported to be formed by the isomerization of (2-nitrobenzylidene)anilines (143) in the presence of sodium bicarbonate (Secareanu and Lupas, 1933).



(143) (144a) (144b)

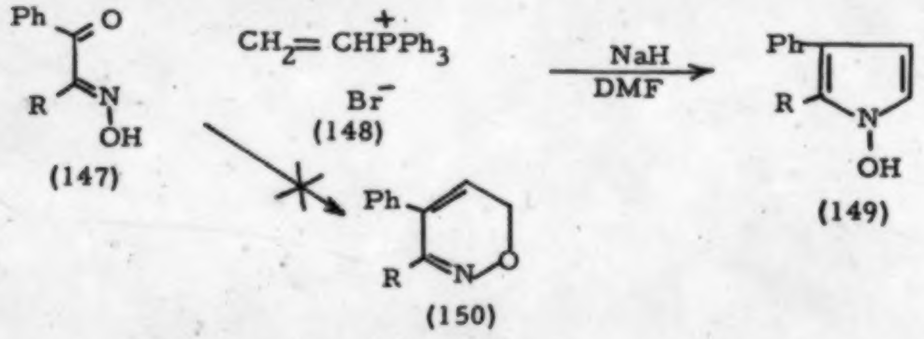
1-Hydroxybenzotriazole (146) was the product of a base-catalyzed cyclization of o-nitrophenylhydrazine (145) (Nietzki and Braunschweig, 1894; Zincke and Schwarz, 1900). This reaction was



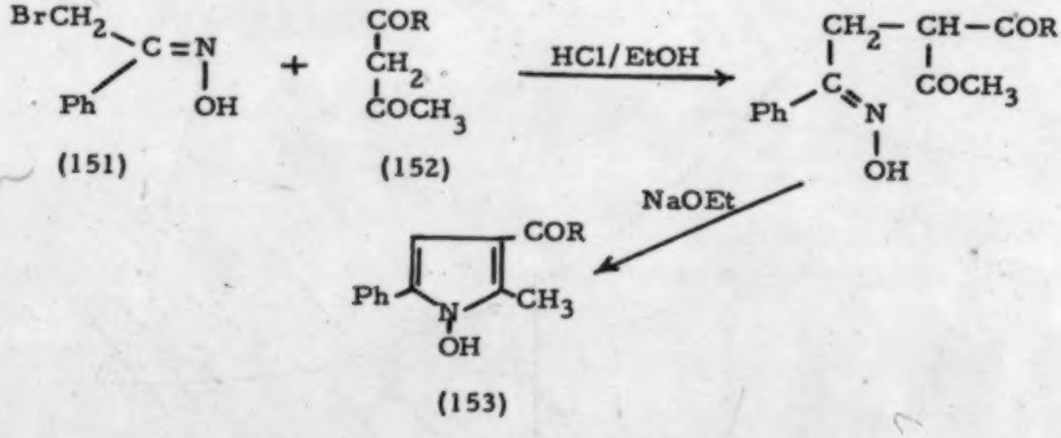
(145) (146a) (146b)

extended to the preparation of 1-hydroxy-6-nitrobenzotriazole by the action of hydrazine hydrate on 2,4-dinitrophenylhydrazine (Curtius and Mayer, 1907). The reaction of hydrazine hydrate with o-halogenonitrobenzenes (Muller and Zimmermann, 1925) or with o-dinitrobenzenes (Vis, 1939) also gave rise to 1-hydroxybenzotriazoles. Yields varied greatly according to the pH of the reaction media (Macbeth and Price, 1934).

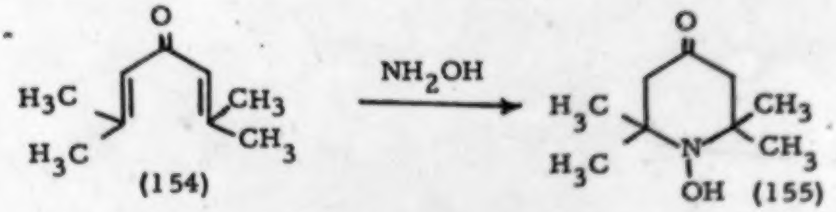
Some monocyclic N-hydroxy compounds can also be prepared by cyclization reactions. The 1-hydroxypyrroles (149) were formed by the condensation of benzil oximes (147) and vinyltriphenylphosphonium bromide (148) in a reaction designed for the preparation of 6H-oxazines (150) (Schweizer and Kopay, 1972). Other substituted


Ph
O
R
N
OH
(147)
CH₂= CHṔPh₃
Br⁻
(148)
NaH
DMF
Ph
R
N
OH
(149)
Ph
R
N
O
(150)

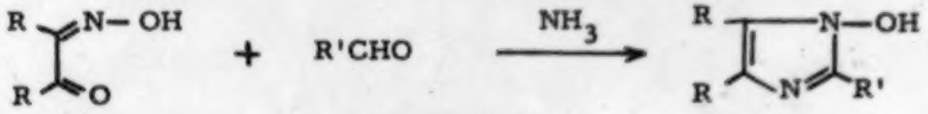
N-hydroxypyrrole derivatives (153) are the products of the reaction of the oxime (151) with various diketones (152) (Spiro and Vaccaro, 1959).


BrCH₂
C=N
Ph
OH
(151)
+
COR
CH₂
COCH₃
(152)
HCl/EtOH
CH₂— CH—COR
C
N
Ph
OH
COCH₃
NaOEt
COR
Ph
N
CH₃
OH
(153)

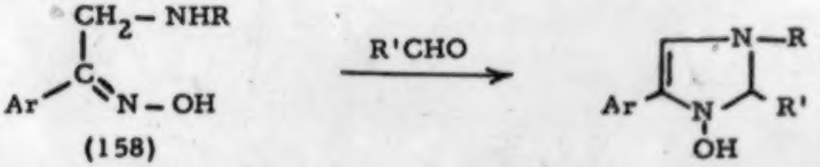
The cyclization of 2,6-dimethylheptadiene-4-one (154) with hydroxylamine offered a means of preparing the 1-hydroxy-4-piperidone derivative (155) (Lehmann, 1897).


NH$_2$OH
H$_3$C
CH$_3$
O
N
OH
(154) (155)

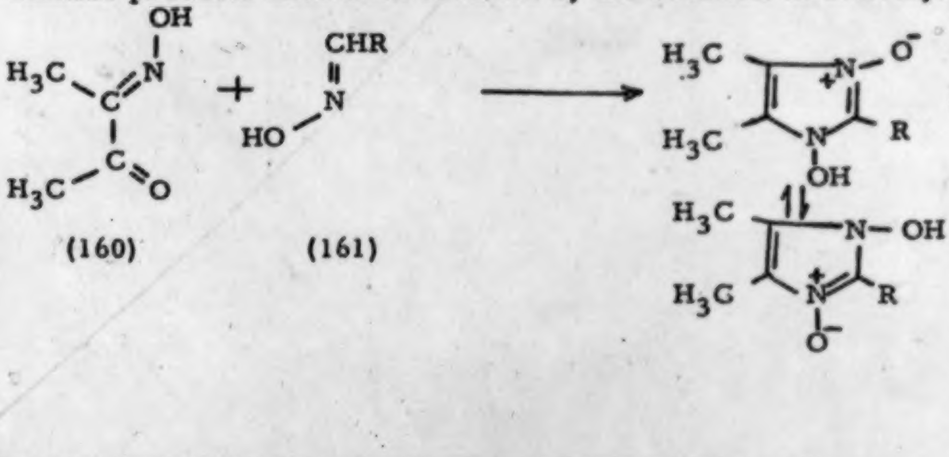
N-Hydroxyimidazoles (157) are formed by the reaction of α-ketoxime (156) with aldehydes in the presence of ammonia (Allan and Allan, 1964; Akagane et al, 1969). This reaction was originally discovered by Diels (1918) but the products were allocated inaccurate structures (Diels and Solomon, 1919). An alternative preparation of

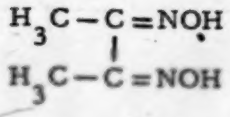

R
N– OH
O
+
R'CHO
NH$_3$
N—OH
N
R'
(156) (157)

this type of compound was achieved by reacting aldehydes with amino-oximes (158) (Busch, 1931; Busch and Kammerer, 1930).


CH$_2$– NHR
C
Ar
N – OH
R'CHO
N—R
R'
N
OH
(158) (159)

Condensation of 2,3-butanedione mono-oxime (160) with aldoximes (161) resulted in the formation of substituted 1-hydroxy-imidazole-3-oxides (162) (Wright, 1964; Bodendoff and Towliati, 1965). Similar products have been obtained by the reaction of dimethyl-

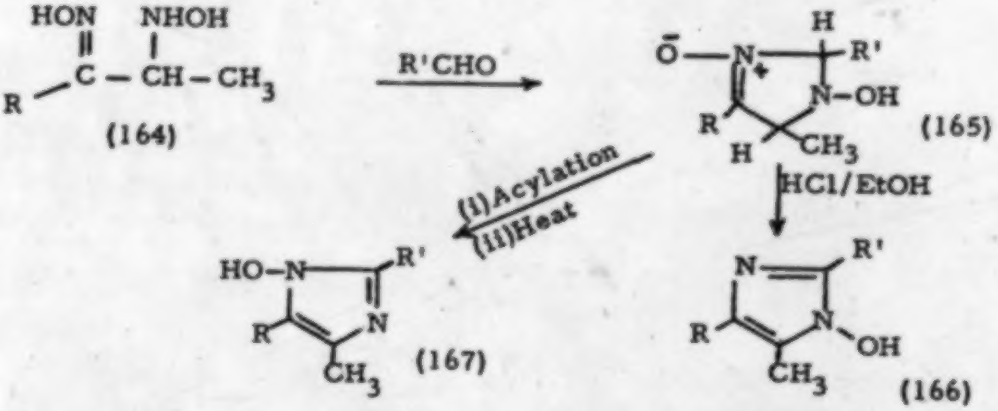

OH
H$_3$C
N
C
O
+
CHR
N
HO
O$^-$
+N
R
OH
N– OH
N
+
O$^-$
(160) (161) (162a) (162b)



(163)

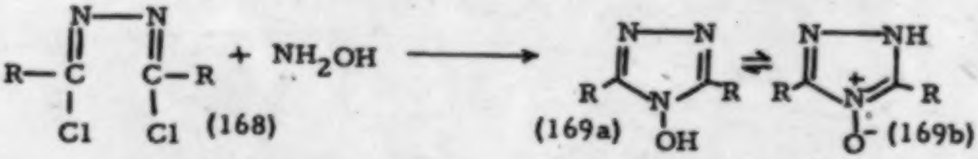
glyoxime (163) with aldehydes (Laparola, 1945).

α-Hydroxylamino-oximes (164) when reacted with aldehydes yield dihydro-1-hydroxyimidazole 3-oxides (165). These compounds were readily converted to hydroxylamines (166) or (167) by acylation followed by heat or by the action of hydrogen chloride in ethanol (Volodarsky et al, 1965).

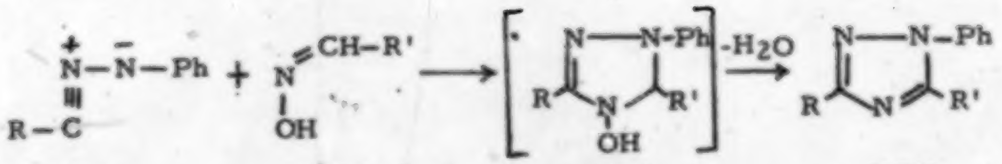


HON
NHOH
R
C – CH – CH₃
(164)
R'CHO
H
O–N+
R'
N-OH
R
H
CH₃
(165)
HCl/EtOH
(i)Acylation
(ii)Heat
HO–N
R'
N
R
CH₃
(167)
N
R'
R
N
OH
CH₃
(166)

4-Hydroxy-1,2,4-triazoles (169) are produced by the reaction of hydroxylamine with dichloro compounds of general structure (168) (Stolle and Thöma, 1906). Also, addition of nitrilimines (170) to the C=N double bond of aldoximes (171) produced 1-hydroxy-4-phenyltriazole (172) but these compounds dehydrated spontaneously to give 1,2,4-triazoles (173) (Huisgen et al, 1965).

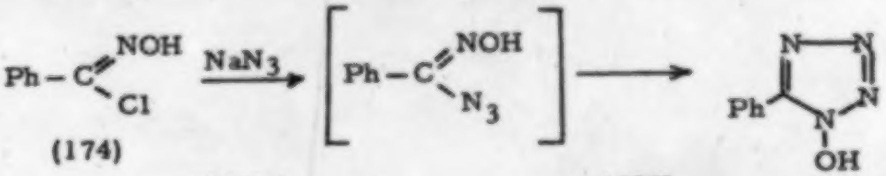


N—N
R—C
C—R
Cl
Cl
(168)
+ NH₂OH
N—N
R
R
N
OH
(169a)
N—NH
R
N+
R
O-
(169b)



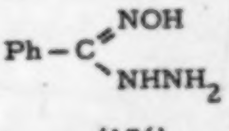
(170) (171) (172) (173)

The reaction between hydroxamoyl chloride (174) and sodium azide gave 1-hydroxy-2-phenyltetrazole(175) (Eloy, 1961). The latter compound was also obtained by the action of nitrous acid on hydroxamoyl hydrazine (176) (Wieland, 1909). Some related derivatives were prepared by the condensation of nitrolic acid (177) with hydrazoic acid (Maffei and Bettinetti, 1956).

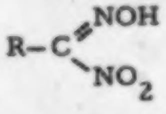


(174)

(175)

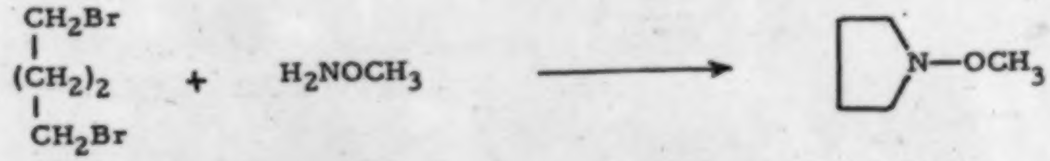


(176)



(177)

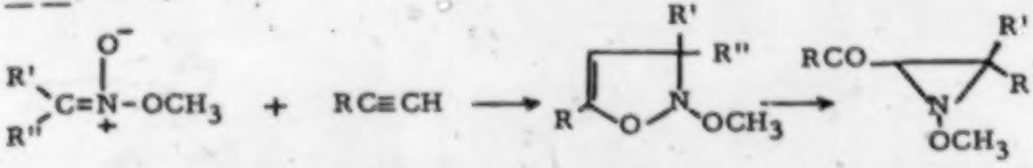
O-Alkyl and O-acyl derivatives of cyclic hydroxylamines are formed by cyclization reactions. Thus, condensation of 1,4-dibromobutane (178) with O-methylhydroxylamine (179) yielded 1-methoxypyrrolidine (180). 1-Methoxypiperidine was similarly prepared from 1,5-dibromopentane (Zinner and Moll, 1966).



(178) (179) (180)

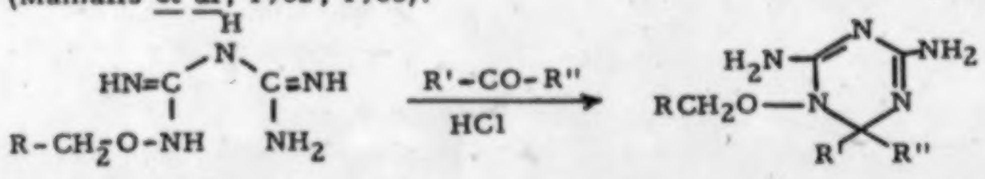
N-Methoxyaziridines of the type (184) were obtained by the reaction of methylnitronates (181) and acetylenes (182); N-methoxy-

4-isoxazolines (183) were postulated as intermediates (Tartakovskii *et al*, 1968).



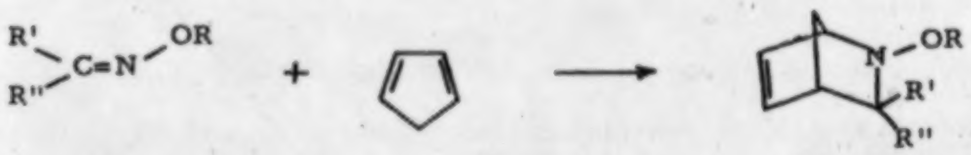
(181) (182) (183) (184)

The N-alkoxy and N-aryloxytriazines (186) can be prepared by the reaction of the diguanid ethers (185) with carbonyl compounds in the presence of hydrochloric acid. Catalytic hydrogenation of (186) gave the parent N-hydroxydihydrotriazine (186, OH for OCH$_2$R) (Mamalis *et al*, 1962, 1965).



(185) (186)

N-Benzoyloxy and N-sulfonyloxy derivatives of 2-azanorbornenes (188) were formed by the addition of cyclopentadiene to various oxime benzoates or sulfonates (187) (Biehler and Fleury, 1968).

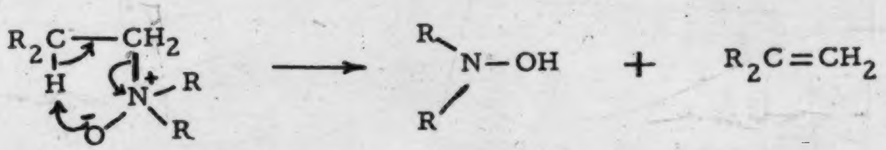


(187) (188)

(E) Miscellaneous Preparations:

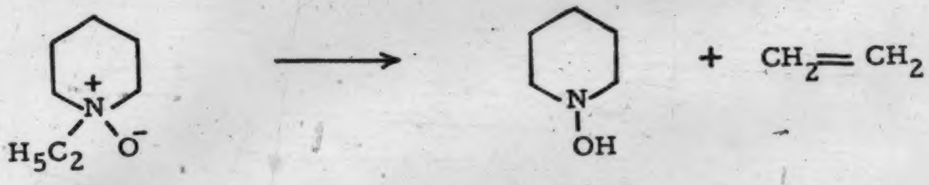
Included under this heading are those preparations which do not fit into any of the preceding classifications.

Certain types of amine oxides such as (189) decompose when heated to yield a hydroxylamine plus an olefin. Examples of this reaction are reported in the early literature (Wernick and Wolffenstein, 1898; Mamlock and Wolffenstein, 1900). An intramolecular mechanism involving a planar, five-membered cyclic transition state was suggested for this reaction (Cope and Trumbull, 1960).


R_2C
CH_2
H
$\overset{+}{N}$
R
R
O
R
N—OH
R
+
$R_2C=CH_2$

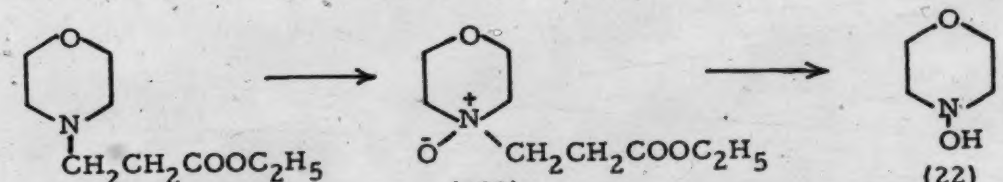
(189)

The early report (Wernick and Wolffenstein, 1898) that N-hydroxypiperidine (23) was obtained by pyrolysis of N-ethylpiperidine oxide (190) was confirmed by Rogers (1955) who extended this


$\overset{+}{N}$
H_5C_2
O^-
N
OH
+
$CH_2=CH_2$

(190) (23)

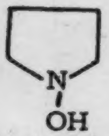
work to the preparation of other N-hydroxy compounds. For example, 1-hydroxymorpholine (22) was obtained by heating the phthalate salt of ethyl β-morpholinopropionate N-oxide (192) with aqueous ammonia. This N-oxide was prepared by the action of monoperphthalic acid on the ester (191). Similarly, 1-hydroxypiperidine (23) was formed


O
N
$CH_2CH_2COOC_2H_5$
O
$\overset{+}{N}$
O^-
$CH_2CH_2COOC_2H_5$
O
N
OH

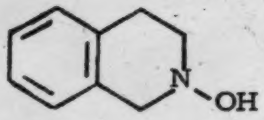
(191) (192) (22)

when ethyl β-piperidinepropionate was treated with perbenzoic acid; in this case, the N-oxide benzoate was not separated. Both these reactions, which were carried out under mild conditions, have been described as a reversal of the Michael addition, facilitated by the formal positive charge on nitrogen (Rogers, 1955).

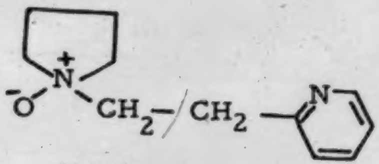
1-Hydroxypyrrolidine (4) and 2-hydroxy-1,2,3,4-tetrahydroisoquinoline (193) were similarly prepared by the pyrolysis of N-ethylpyrrolidine N-oxide (Thesing and Sirrenberg, 1959) and N-(carbethoxyethyl-1,2,3,4-tetrahydroisoquinoline) N-oxide (Thesing and Mayer, 1957) respectively. Compound (4) was also obtained by the pyrolytic decomposition of the N-oxide (194) under reduced pressure (Paquette, 1962).



(4)

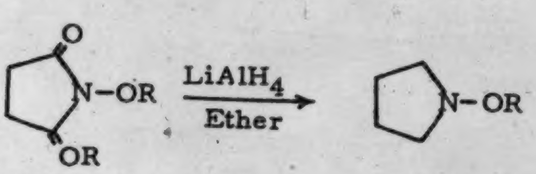


(193)



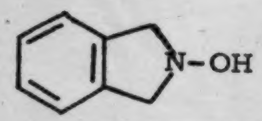
(194)

Some cyclic hydroxylamines are prepared by chemical modification of compounds which already have the N-hydroxy function. For example, lithium aluminum hydride reduction of N-hydroxysuccinimide (195a) and its O-methyl analog (195b) yielded the corresponding derivatives of pyrrolidine (196) (Zinner and Moll, 1966). Similar reduction of 3-hydroxyphthalimide gave N-hydroxyisoindoline (197) (Zinner and Dueerkop, 1969).



(195)

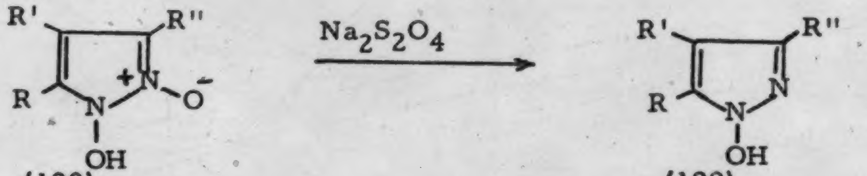
(196)



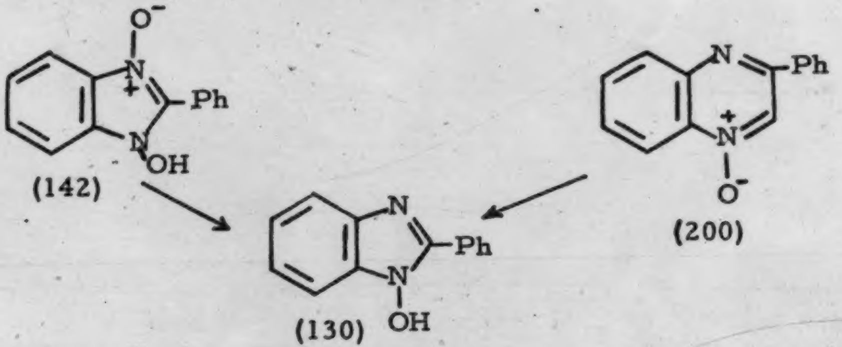
(197)

a, R= H b, R=CH_3

Also, mild reduction of 1-hydroxypyrazole 2-oxides (198) with sodium dithionite yielded 1-hydroxypyrazoles (199); zinc and acetic acid reduced both the N-oxy and N-hydroxy functions (Freeman and Gannon, 1969). Similarly, cautious reduction of the dioxy derivative (142) with stannous chloride and hydrochloric acid resulted in the formation of 1-hydroxy-2-phenylbenzimidazole (130) (Minsci *et al*, 1963). The latter N-hydroxy compound was said to be formed by the action of alkaline hydrogen peroxide on 2-phenylquinoxaline 4-oxide (200) (Hayashi and Iijima, 1962).

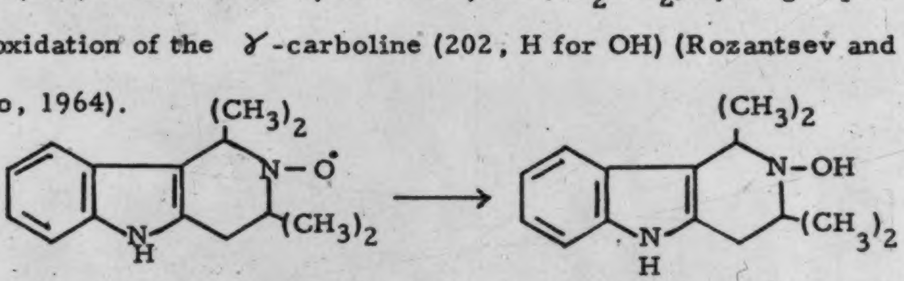


(198) (199)



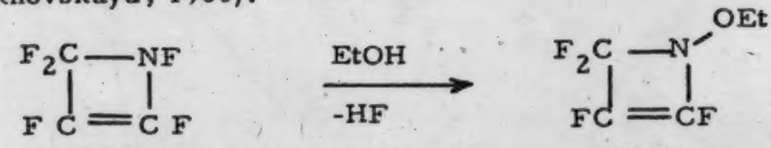
(142) (130) (200)

Reduction of the stable free radical (201) with phenylhydrazine or with hydrogen over platinum yielded 2,2,4,4-tetramethyl-1,2,3,4-tetrahydro-3-hydroxy-γ-carboline (202). The radical (201) was obtained by the catalyzed (Na_2WO_2) hydrogen peroxide oxidation of the γ-carboline (202, H for OH) (Rozantsev and Shapiro, 1964).



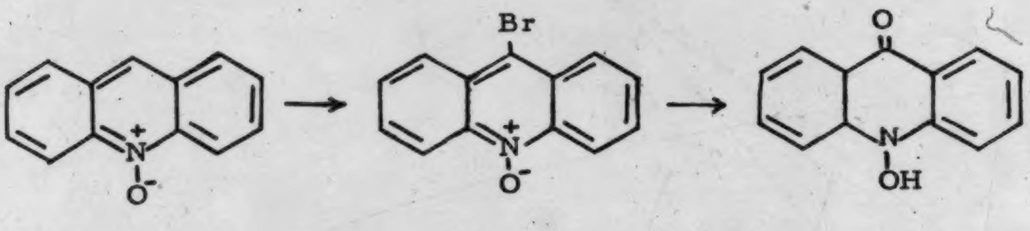
(201) (202)

The reaction of ethanol with the pentafluoro compound (203) causes elimination of one molecule of hydrogen fluoride and the formation of 1-ethoxyaza-2-cycloperfluorobutene (204) (Knunyants and Bykhovskaya, 1960).



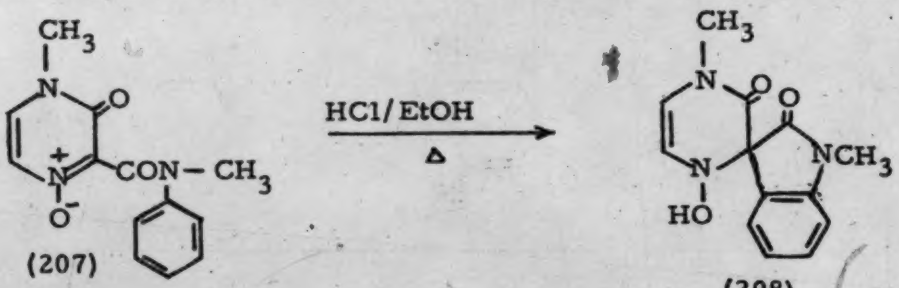
(203) (204)

10-Hydroxyacridone (108) was prepared by acid hydrolysis of 9-bromoacridine 10-oxide (206) which in turn was obtained by the bromination of acridine-10-oxide (205) in acetic acid (Acheson et al, 1960).



(205) (206) (108)

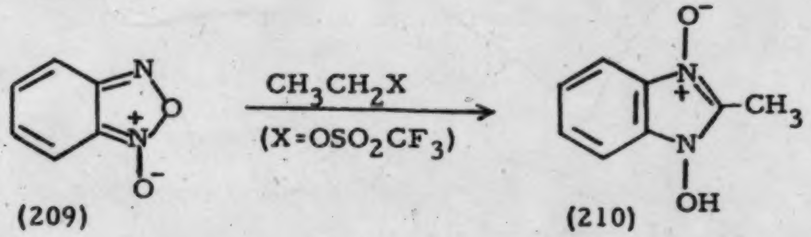
Heating the pyrazine N-oxide (207) with ethanolic hydrogen chloride offered the hydroxylamino-spirolactam (208). This compound is believed to be formed by the protonation of the N-oxide followed by intramolecular electrophilic substitution at the o-position



(207) (208)

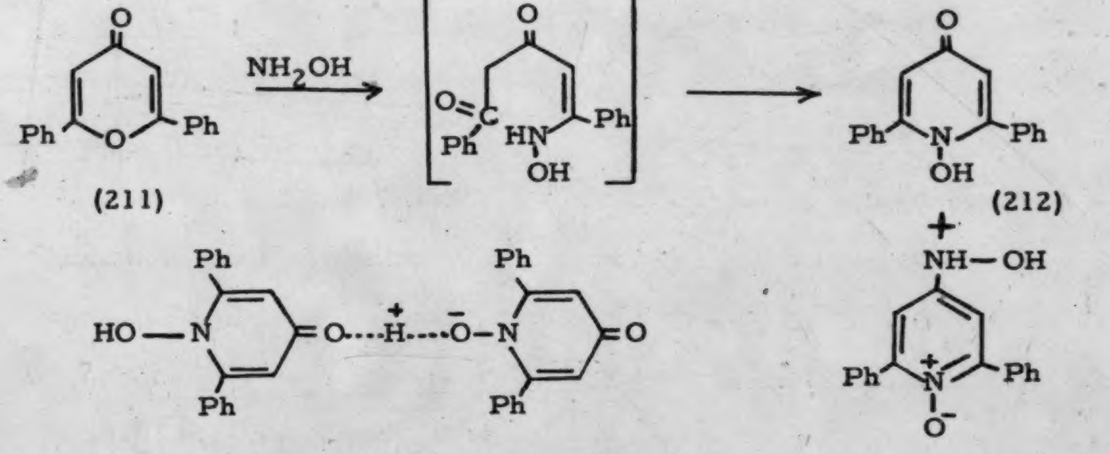
of methylanilide by the pyrazine 2-C-atom (Habib and Rees, 1962).

Alkylation of benzofuroxan (209) with the powerful alkylating agent, methyl trifluoromethane sulfonate resulted in the isolation of the methylbenzimidazole (210) rather than the expected quaternary salt. A mechanism for this rearrangement was suggested by Boulton et al (1966, 1967).


N
O
$\overset{+}{N}$
O^-
CH_3CH_2X
$(X=OSO_2CF_3)$
O^-
$\overset{+}{N}$
CH_3
N
OH

(209) (210)

Condensation of 2,6-diphenyl-4-pyrone (211) with hydroxylamine resulted in ring opening and then reclosure to give 1-hydroxy-2,6-diphenyl-4-pyridone (212) and 4-hydroxylamino-2,6-diphenylpyridine 1-oxide (213). The i.r. spectrum of (212) in chloroform showed that it exists exclusively as the N-hydroxy form (212). On the other hand, the solid spectrum suggested a polymeric association (214) (El-kholy et al, 1962).


O
Ph
O
Ph
NH_2OH
O
O=C
Ph
HN
OH
Ph
O
Ph
N
OH
Ph
+
NH—OH
Ph
$\overset{+}{N}$
Ph
O^-
Ph
HO—N
=O····$\overset{+}{H}$····$\overset{-}{O}$—N
=O
Ph
Ph
Ph

(211) (212) (214) (213)

3. PHYSICAL AND CHEMICAL PROPERTIES OF CYCLIC HYDROXYLAMINES

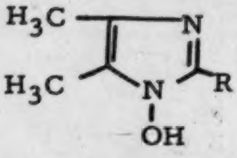
The physical and chemical properties of cyclic hydroxylamines are related to those of their parent amines, but the presence of the N-hydroxy function also permits a number of reactions analogous to those found with arylhydroxylamines. There are also some similarities between the chemical reactivity of cyclic hydroxylamines and cyclic hydroxamic acids although the presence of a carbonyl function in the α-position of the latter may have profound effects on their solubility as well as on their chemical behavior. Also, in cases where the cyclic N-hydroxy compound exists in tautomeric equilibrium with the corresponding N-oxide, the properties demonstrated might be related to those of the N-oxides.

(A) Solubility and Salt Formation:

Solubility in water or organic solvents is influenced by the nature of the heterocyclic system incorporating the N-hydroxy function. However, solubility in alkalis or acids could be modified considerably by the introduction of this function. In many cases, N-hydroxy compounds are acidic and, therefore, soluble in alkali solutions. Stable sodium salts (Loudon and Tennant, 1960; Freeman and Gannon, 1969) as well as potassium, anilinium and hydrazinium salts (Curtius and Mayer, 1907) of some cyclic hydroxylamines have been prepared and identified. Insoluble copper salts of 1-hydroxyisoxazolidines (Kohler and Barrett, 1924, 1926) and insoluble silver salts of 1-hydroxybenzotriazole (Brady and Day, 1923) are also known. The latter compounds have been used analytically for the determination of silver

(Singh and Kapil, 1960; Deorha and Soreen, 1964; Sharma and Mukerji , 1965). 1-Hydroxypyrazole 1-oxides form chelates with Cu^{+2}, Co^{+2}, Cd^{+2} and Ni^{+2} (Freeman and Gannon, 1969).

Some cyclic N-hydroxy compounds are basic enough to form acidic salts. For example, 1-hydroxypiperidine and 1-hydroxymorpholine were isolated as hydrochlorides, picrates and acid oxalates (Rogers, 1956; Zinner and Kliegel, 1966). The third group of cyclic hydroxylamines contains compounds which are virtually neutral and form no salts. Examples are 1-hydroxy-2-phenylpiperidine (Kato and Yamanaka, 1965) and 1-hydroxy-2-methylindole (Acheson et al, 1970). Minor changes in structure sometimes alter the acidity and the solubility characteristics of N-hydroxy compounds. For example, 1-hydroxyimidazole (215, R=Ph) is amphoteric (pK_a 9.41, pK_b 9.36) while other 1-hydroxyimidazoles such as (215, $R=CH_3$) are not (Akagane et al, 1969).



(215)

(B) Qualitative and Quantitative Determination:

Cyclic hydroxylamines readily reduce Tollen's and Fehling's solutions (Jones and Major, 1927; Habib and Rees, 1962; Feigl, 1966). The former reagent is used as a spray for the detection of N-hydroxy compounds on thin-layer chromatographic plates (Beckett and Salami, 1972). Some cyclic hydroxylamines also give a positive test with Schiff reagent (Zinner, 1957). Some of these compounds form a red color when treated with ferric chloride but not as spontaneous as that obtained by hydroxamic acids with the same reagent. In fact, this color results from the oxidation of cyclic hydroxylamines to the corresponding hydroxamic acids (Elsworth and Lamchen, 1966). N-hydroxyindoles are said to give a green color with ferric chloride solution and also a stronger color with sodium 2-naphthol-4-sulfonate than do the corresponding indoles (Kawana et al, 1965).

A more specific spot test for hydroxylamines, including the cyclic ones, is provided by reaction with triphenyltetrazolium chloride (T.T.C.) which, in the presence of alkali, give a characteristic purple-red color. This seems to be a specific reaction (Snow, 1954) and by its means the presence or absence of hydroxylamine can usually be safely deduced (Rogers, 1955). These investigators and others (Zinner and Kliegel, 1966; Thesing and Sirren, 1959; Brown et al, 1959) used this test to follow the progress of reactions which involve hydroxylamines. Feigl (1966), however, considers hydroxylamine to be completely inactive towards this reagent. It should also be remembered that other substances, such as sugars and ascorbic acid give a positive test with T. T. C. (Feigl, 1966).

The separation of some cyclic hydroxylamines from their corresponding amines as well as from some related nitroxides can be achieved by means of thin-layer chromatography. Weil (1968) developed some useful solvent systems for this purpose. Iodine vapor or potassium permanganate solution were used for detection and were found to be more useful than T. T. C. which gave only very faint pink spots.

Although a number of methods have been developed for quantitative estimation of aryl hydroxylamines (Boyland and Nery, 1964;

1964 a) and hydroxamine acids (Nery, 1966; Roncucci et al, 1971), there is as yet no general method for analysis of cyclic hydroxylamines, However, it is possible that these compounds could be determined quantitatively by gas-liquid chromatography, after conversion into suitably volatile ethers.

(C) Molecular Spectroscopy and Mass Spectrometry:

Ultraviolet spectroscopy: This technique was used by several investigators (e.g.: Mcbeth and Price, 1936; Takahashi and Kano, 1963; Stacy et al, 1966) to study the tautomerism of cyclic N-hydroxy compounds. In such cases, the position of maxima as well as their intensities were compared with "fixed" models in which tautomerism was not possible. Kawana et al (1965) also used the bathochromic shift (5-10 mμ) showed by N-hydroxyindole derivatives, on addition of alkali, as a method for confirming the presence of the N-hydroxy function.

Infrared spectroscopy: This has proven to be more useful for both identification purposes and tautomeric studies. Mousseron-Canet and Boca (1967) as well as Kawana et al (1965) studied the i.r. spectra of some 1-hydroxyindoles and found evidence for the existence of intermolecular hydrogen bonding. The simple compounds, N-methyl and N,N dimethylhydroxylamine were also strongly hydrogen bonded (Mansel and Spiers, 1959).

The presence of either or both the N-hydroxy and N-oxy tautomers in any compound could be readily deduced from its infrared spectrum and this was used to assign tautomeric equilibria in different systems (Katritzky and Jones, 1960; Kloetzel et al, 1957; Mousseron-Canet and Boca, 1967). Distinction between the N-OH and C-OH functions is probably more difficult since both absorptions seem to be affected similarly by the same parameters (table 1). Their acetates or benzoates, however, are of particular advantage for identification purposes since electronegative groups attached to the oxygen atom of carboxylic acids are known to raise the stretching frequency of the carbonyl group by 15-70 cm^{-1} depending on the group (Freeman, 1958). The most pronounced shifts were observed with hydroxamic acids but also all compounds where the oxygen substituent was attached to nitrogen showed abnormally high frequency carbonyl absorptions. As expected, the N-benzoate esters absorb at a lower frequency (~1770 cm^{-1}) than the N-acetate (~1800 cm^{-1}) but still much higher than the ordinary benzoates (~1720 cm^{-1}) (see table 1).

Nuclear magnetic resonance spectroscopy; This technique has been employed more frequently for detecting the N-hydroxy function as well as for studying the tautomerism of N-hydroxy compounds (Bonnet and McGreer, 1962; Acheson et al, 1968, 1970; Schweizer and Kopay, 1972). Also Mousseron-Canet and Boca (1967) used this method for quantitative determination of both tautomers of some N-hydroxyindole derivatives.

With few exceptions, studies showed that the N-hydroxy-proton resonance is detected at low field even in the absence of intramolecular hydrogen bonding (table 1). Acheson et al (1970) detected the N-hydroxy proton in 1-hydroxy-2-methylindole at $\delta \sim 9.00$ and reassigned the resonance at $\delta \sim 6.00$, attributed earlier (Mousseron-Canet and Boca, 1967) to this proton, to the 3-hydrogen atom of the indole. The N-methoxy function might also be detected with n.m.r. spectroscopy since the methoxy group is attatched to an electro-

Table 1: Infrared absorption maxima and n.m.r. chemical shifts (relative to TMS) of some cyclic hydroxylamines and their methyl and acyl derivatives.

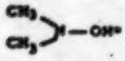
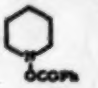
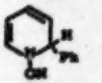
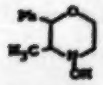
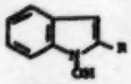
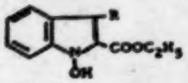
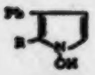
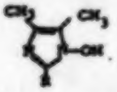
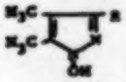
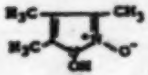
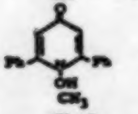
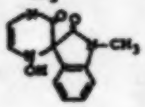
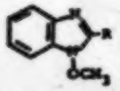
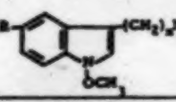
Structure	ν		δ		Ref.
	OH	C=O (ester)	OH	OCH_3	
 $(CH_3)_2N{-}OH$*	3600-3000				1
, benzoate*		1760			2
		1762 (liq)			2
		1766 (CCl_4)			3
	3600-2400 (small)		8.72 ($CDCl_3$)		4
			9.2		5
, benzoate		1739			6
		1735			4
	3600		3.3		7
					
R= CH_3	3510-3490 ($CHCl_3$)		~6.00		8
	3450 (KBr)				8
			9.75		9
			8.3-8.94		9
, p-chlorobenzoate		1775			10
R= Ph	2400, 3250 (br.)		8.85 ($CDCl_3$)		11
	2430 (v.br.)				12
, acetate		1772			11
, benzoate		1760			13
R= COOH	3225				11
, acetate		1800			11
, benzoate		1783			11
R= $COOCH_3$	3100				11
				4.2	14
, acetate		1802			14
, benzoate		1778			11
					
R= CN	3260				15
			9.5-10.5 (dimsol)		9
R= $CONH_2$	3350, 3150				15
, acetate		1800			15
					
R= Ph	3320 (nujol)		not detected ($CDCl_3$)		16
, acetate		1700 (nujol)			16
, benzoate		1750 (nujol)			16

Table I: Continued

Structure	ν		δ		Ref.
	OH	C=O (ester)	OH	OCH_3	
$R = COOC_2H_5$	3370 (nujol)		10.2 ($CDCl_3$)		16
R = H			10.1 ($CDCl_3$)		16
			13.35 ($CDCl_3$)		17
, benzoate		1730			18
			8.5		19
, p-nitrobenzoate		1790			20
			15.6		21
	3636 ($CHCl_3$)				22
	3320				23
				4.1-4.2 ($CDCl_3$)	24
				4.09	25
				3.99	26

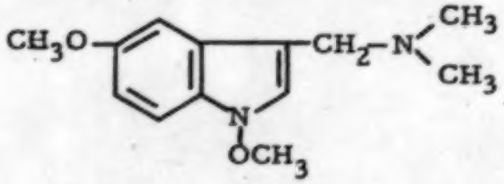
* are presented here for comparison.

References:

(1) Manoel and Spiers (1959)
(2) Freeman (1958)
(3) Zinner (1958)
(4) Coutts and El-hawari (unpublished)
(5) Kato and Yamanaka (1965)
(6) Kato et al (1967)
(7) Bouhett and Salami (1972)
(8) Mousseron-Canet and Boca (1967)
(9) Acheson et al (1968)
(10) Acheson et al (1970)
(11) Kawana et al (1965)
(12) Sundberg (1969)
(13) Louden and Tennant (1960)
(14) Baxter and Swan (1967)
(15) Louden and Wellings (1960)
(16) Schweizer and Kopay (1972)
(17) Allan and Allan (1964)
(18) Akagane et al (1969)
(19) Freeman and Gannon (1966)
(20) Freeman et al (1969)
(21) Freeman and Gannon (1969)
(22) El-holy et al (1962)
(23) Habib and Rees (1962)
(24) Takahashi and Kano (1964)
(25) Morimoto and Oshio (1965)
(26) Johns et al (1967)

negative atom. In the few reported examples (Table 1), the N-methoxy-protons resonate at a lower field (δ 4-4.2) than usually demonstrated by aromatic ethers ($\delta \sim 3.8$).

Mass spectrometry: Some cyclic N-hydroxy compounds were identified by their ability to lose $OH^{\cdot}$ radicals from their molecular ions (Acheson et al, 1970; Beckett and Salami, 1972; Schweizer and Kopay, 1972). A similar loss resulting from N-O bond cleavage might also be expected from O-substituted derivatives of N-hydroxy compounds but the indole (20) showed only a small fragment ion (3%) corresponding to the direct loss of OCH_3 radical from the molecular ion. However, the same spectrum demonstrated a strong peak due

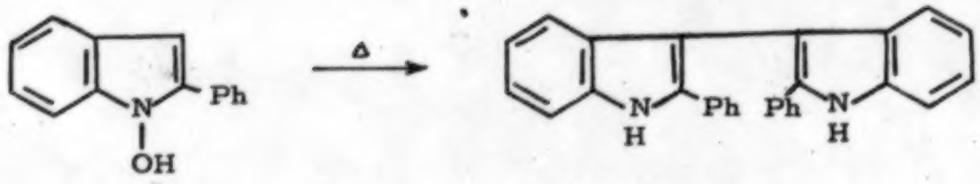


(20)

to the loss of OCH_3 from the $(M\text{-}NMe_2)^{+}$ ion. It is probable that this methoxy radical originated from the N-methoxy function and not from the aromatic ring (Johns et al, 1967).

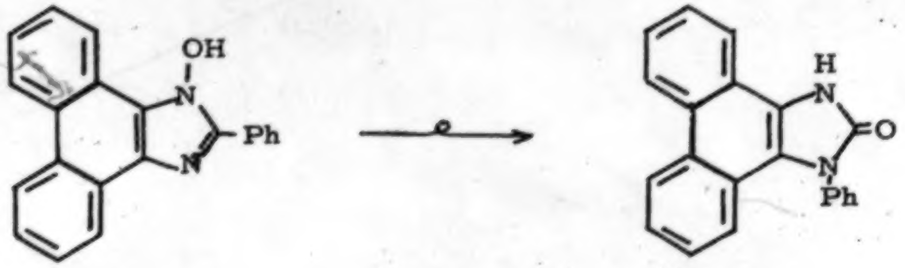
(D) Stability:

Cyclic hydroxylamines and their alkyl and acyl derivatives vary greatly in their stability. Some show surprising stability and are isolated readily while others are very difficult to isolate and undergo oxidation, dehydration or rearrangement. Many of these compounds also dimerize, dehydrate or rearrange when heated with or without solvent. Thus, in refluxing cymene, 1-hydroxy-2-phenylindole (83) was converted to the dimeric indole (216) (Sundberg, 1965). Also,


N
Ph
OH
Δ
N
H
Ph
Ph
N
H

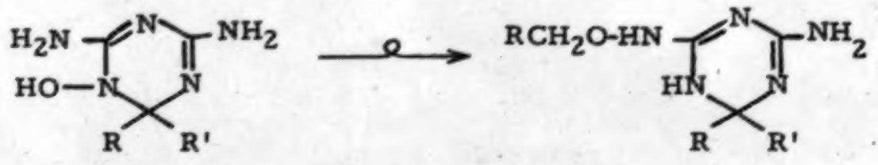
(83) (216)

heating 1-hydroxy-2-phenyl-1,2-dihydropyridine (62a) to 200° or boiling it with acetic anhydride resulted in dehydration to 2-phenylpyridine (Kato and Yamanaka, 1965). The N-hydroxyimidazole (217) rearranged to the imidazolone (218) upon heating to 235° (Volkamer and Zimmermann, 1969).


OH
N
Ph
N
H
N
O
N
Ph

(217) (218)

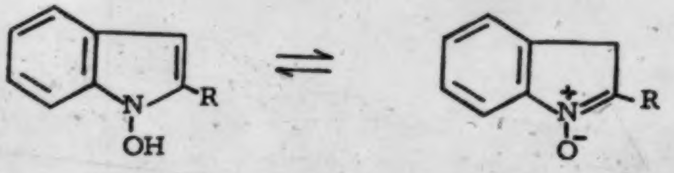
Upon alkylation, some N-hydroxydihydrotriazines (17) yielded rearrangement products (219). When the N-alkoxy derivatives (17, OCH$_2$R for OH) were isolated, they converted smoothly into (219) by heating with or without solvent. The N-hydroxy compounds (17) did not rearrange on heating (Mamalis et al, 1965).


H2N
N
NH2
HO
N
N
R
R'
RCH2O-HN
N
NH2
HN
N
R
R'

(17) (219)

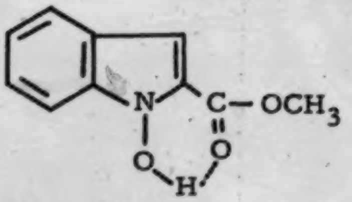
LEAF 52 OMITTED IN PAGE NUMBERING.

The tautomeric behavior of some N-hydroxyindoles (7) was studied by Mousseron-Canet and Boca (1967). N-Hydroxyindole (7, R=H) itself was found to exist solely as 3H-indole N-oxide (7b) whereas the 2-substituted derivatives(7, R=CH_3 or Ph) were tautomeric mixtures.

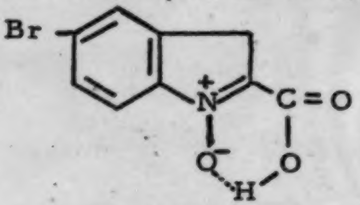


(7a) (7b)

The N-oxide form (7b) is favored in solvents which are capable of strong hydrogen bonding. For 1-hydroxy-2-methylindole (7, R=CH_3), the proportion of each tautomer has been quantitatively estimated from the n.m.r. methyl integral. In deuterochloroform, methyl 1-hydroxyindole-2-carboxylate (224) exists as such while 5-bromo-1-hydroxyindole-2-carboxylic acid is present entirely in the 1-oxide form (225) in the same solvent. These results were attributed to intramolecular hydrogen bonding (Acheson *et al*, 1968).

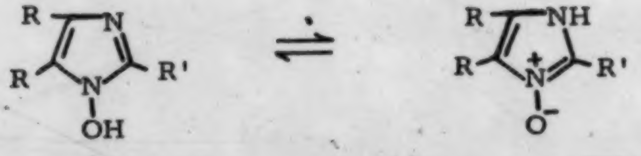


(224)



(225)

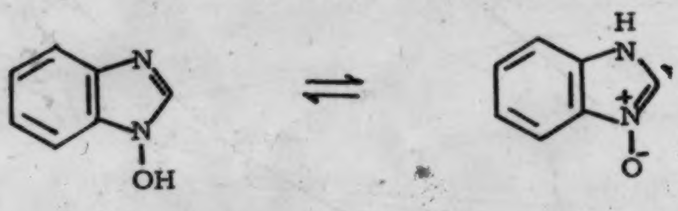
Similar studies have been reported on the tautomerism of 1-hydroxypyrroles (Kloetzel *et al*, 1957; Bonnett and McGreer, 1962; Schweizer and Kopay, 1972), 1-hydroxyimidazoles (Akagane *et al*, 1969), tetrahydropyridine 1-oxides and dihydro-1,4-oxazine 4-oxides (Elsworth and Lamchen, 1968). The two tautomers (157a ⇌ 157b) of certain triaryl-1-hydroxyimidazoles were claimed to be isolated under



(157a) (157b)

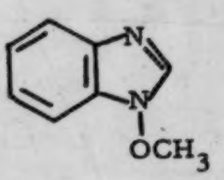
controlled conditions (Volkamer and Zimmermann, 1969).

The structure of 1-hydroxybenzimidazole (226) evoked some controversy. Kew and Nelson (1962) suggested the N-oxide form

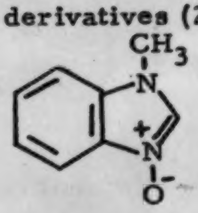


(226a) (226b)

(226b) for this compound but Takahashi and Kano (1963) showed, by using u.v. spectroscopy that a solvent-dependent tautomeric equilibrium (226a $\rightleftharpoons$ 226b) existed between the two forms. Hayashi et al (1960) reported earlier what was considered to be a chemical evidence for such tautomerism; reaction of 1-hydroxybenzimidazole (226) with diazomethane yielded a mixture of the alkyl derivatives (227) and (228).

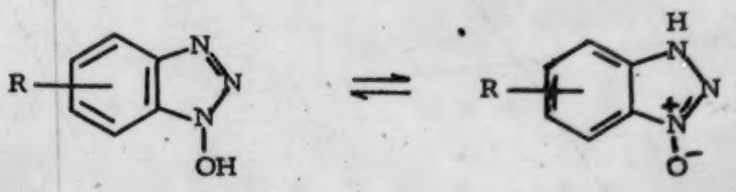


(227)



(228)

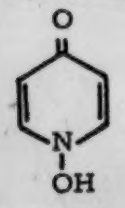
A solvent-dependent tautomerism was also observed with 1-hydroxy-6-nitrobenzimidazole (Neadle and Pollitt, 1967) while 1-hydroxy-2-phenylbenzimidazole was shown to exist entirely as the N-hydroxy form even in aqueous solution (Stacy et al, 1966). 1-Hydroxybenzotriazole derivatives (229a) also behaved similarly; some are tautomeric



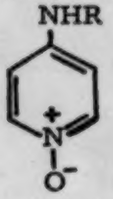
(229a) (229b)

mixtures (229a ⇆ 229b) while others exist only as the N-hydroxy structure (229a) (Macbeth and Price, 1936).

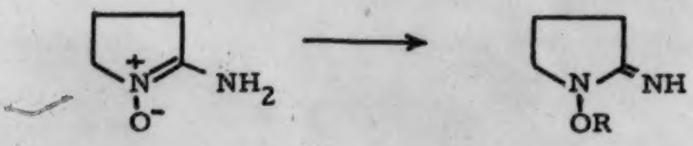
Studies using physical methods indicated that both tautomers of 1-hydroxy-4-pyridone (230) are of comparable importance (Katritzky and Logowski, 1971a). Similarly, 10-hydroxyacridone exists in equilibrium with equal amounts of 9-hydroxyacridine 10-oxide (Ionescu et al, 1966). In contrast, amino N-oxide exist predominantly in the amino form (231) (Katritzky and Logowski, 1971b). In certain instances, however, chemical reactions gave products derived from the N-hydroxy tautomer of amino N-oxides. Alkylation and benzoylation of 2-aminopyrroline 1-oxide (232) occurred at the oxygen atom giving products of the type (233) while acetylation gave only the N-acetyl derivative (Forrester and Thomson, 1963).



(230)



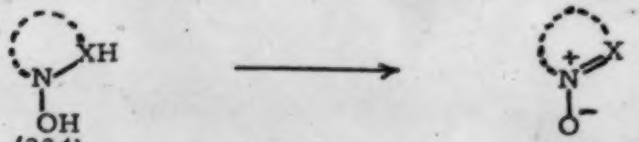
(231)



(232) (233)

(F) Oxidation:

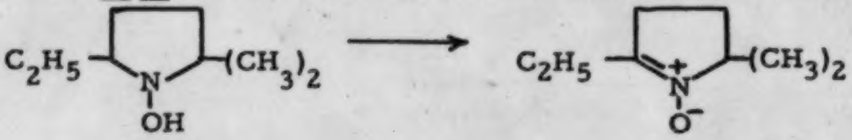
Cyclic hydroxylamines are readily oxidized by a wide variety of oxidizing agents. When an α-hydrogen is available, the products are mostly cyclic nitrones (235); otherwise, different



(234) (235)

products are isolated.

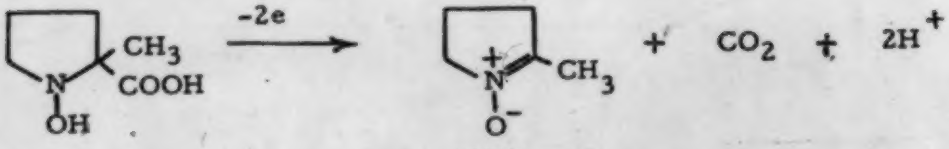
The passage of oxygen (or air) into a solution of the N-hydroxy compound, in the presence of a catalyst such as copper-ammonia complex, is commonly employed, but sometimes fails to oxidize these compounds. This method was used for the oxidation of 1-hydroxypyrrolidines such as (236) to the corresponding nitrones (237) (Bonnett et al, 1959). Similar results were obtained when



(236) (237)

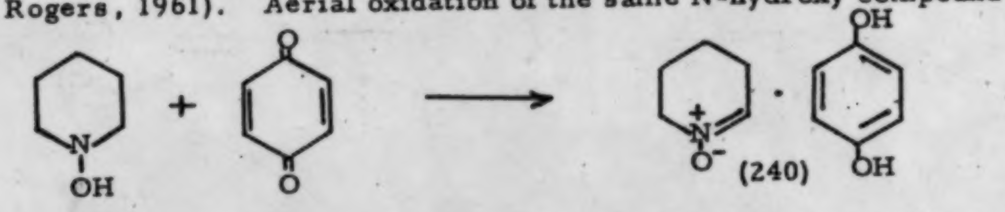
alkaline potassium ferricyanide (Brown et al, 1959b) or yellow mercuric oxide (Thesing and Sirrenberg, 1959) were used as oxidizing agents. The latter reagent was also employed for the oxidation of N-hydroxypiperidine, N-hydroxymorpholine (Elsworth and Lamchen, 1968), 2-hydroxy-1,2,3,4-tetrahydroisoquinoline (Thesing and Mayer, 1957) and 1-hydroxybenzodiazepines (Sternbath and Reeder, 1961; Sulkowski and Childress, 1963; Hoffman-LaRoche, 1966) to the corresponding nitrones.

Other ring substituents can also be affected during the oxidation of the N-hydroxy function. 1-Hydroxy-2-methylpyrrolidine-2-carboxylic acid (238) undergoes oxidative decarboxylation during the nitrone (239) formation (Brown et al, 1959).



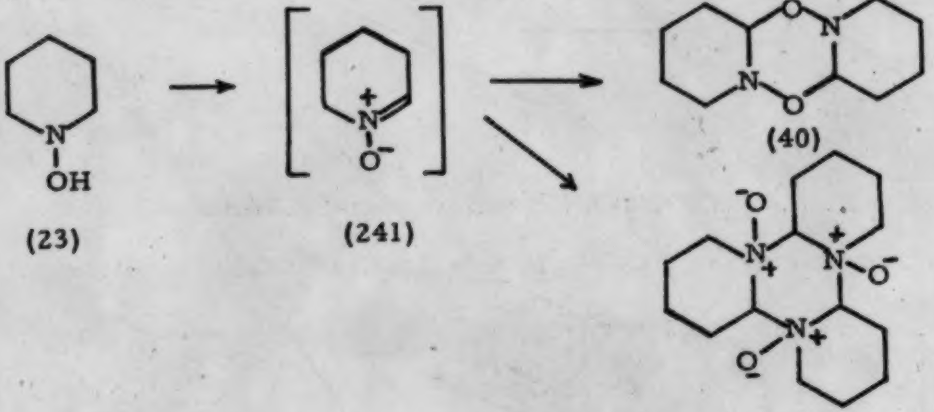
(238) (239)

1-Hydroxypiperidine (23) reacted with p-benzoqunione to yield a tetrahydropyridine 1-oxide-hydroquinone adduct (240) (Brown and Rogers, 1961). Aerial oxidation of the same N-hydroxy compound



(240)

in the presence of cupric acetate yielded 3,4,5,6-tetrahydropyridine 1-oxide (241) which dimerizes immediately to the cyclic dimer (40) (Thesing and Mayer, 1956). A trimer formulated as (41) was formed by the oxidation of (23) using potassium ferricyanide (Thesing and Mayer, 1957). Related polymers were obtained by the oxidation of



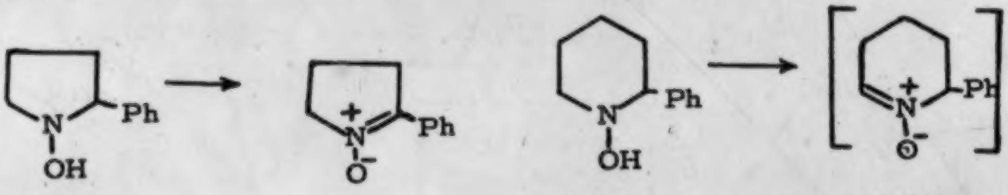
(40)

(23) (241)

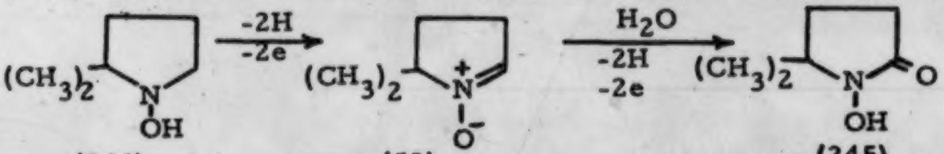
(41)

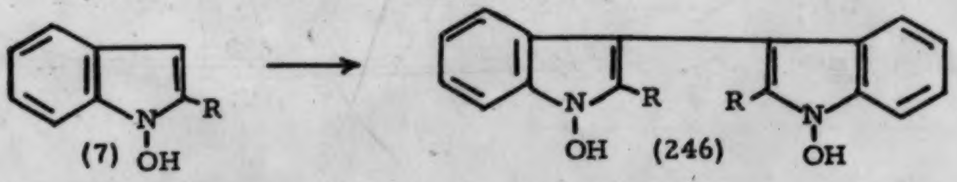
N-hydroxyhexaethyleneamine (Alford et al, 1966) and N-hydroxymorpholine (Elsworth and Lamchen, 1968).

In some cases, the course of oxidation was found to depend on subtle steric effects. Oxidation of 1-hydroxy-2-phenylpyrrolidine (55) with mercuric oxide gave the nitrone (241) in which the nitrone group is conjugated with the phenyl group (Thesing and Mayer, 1957, Thesing and Sirrenberg, 1958). In contrast, the same reagent oxidized 1-hydroxy-2-phenylpiperidine (242) to a dimer of the nitrone (243) in which the nitrone group and the phenyl group are not conjugated (Thesing and Mayer, 1957). This difference in the behavior of the analogous N-hydroxy compounds (55) and (242) was explained in terms of their stereochemistry (Thesing and Sirrenberg, 1959).

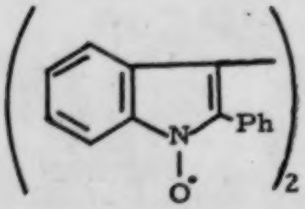

(55) (241) (242) (243)

Ferric chloride is reported to oxidize the hydroxylamine (244) to the corresponding hydroxamic acid (245) *via* the intermediate (52) (Elsworth and Lamchen, 1966). The same reagent oxidized ethyl 1-hydroxyindole-2-carboxylate (7, R=COOEt) to the bis N-hydroxy compound(246, R=COOEt) (Gabriel *et al*, 1923). A related product (246, R=Ph) was obtained by the oxidation of 1-hydroxy-2-phenylindole (7, R=Ph) with nitrobenzene (1 mole) or diethylazodicarboxylate (2.5 mole) (Colonna and Monti, 1962). The diradical (247) was formed


(244) (52) (245)


(7) (246)

when (7, $R = Ph$) was treated with t-butyl hydroperoxide or diethylazodicarboxylate. Oxidation with excess nitrobenzene gave in addition to (247), another diradical (248) and a nitrone (249) (Colonna and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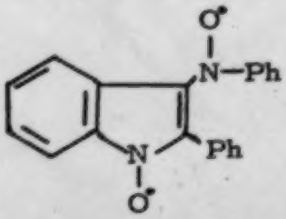
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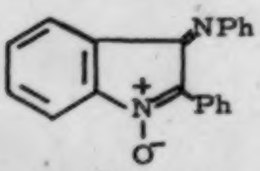
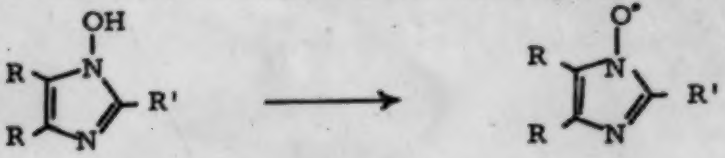
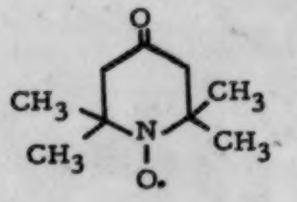

(249)

De Martino, 1963; Colonna and Bruni, 1964, 1965).

Other cyclic hydroxylamines are also reported to yield free radicals on oxidation. 1-Hydroxyimidazole (157) gave the radical (250) on treatment with halogens in polar solvents or with lead dioxide


(157) (250)

(Volkamer *et al*, 1967; Volkamer and Zimmermann, 1969). The stable free radicals (251) and (201) were also obtained by the silver oxide (Rozantsev and Neiman, 1964) and catalyzed (Na_2WO_2) hydrogen peroxide (Rozantsev and Shapiro, 1964) oxidation of the corresponding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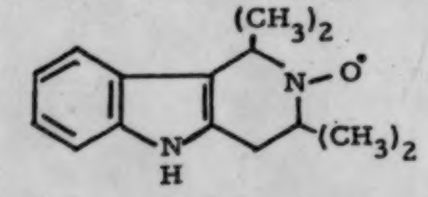
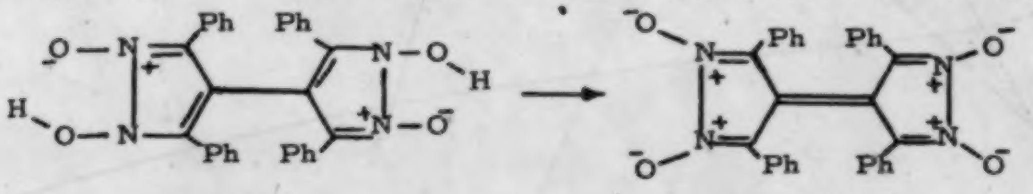

(201)

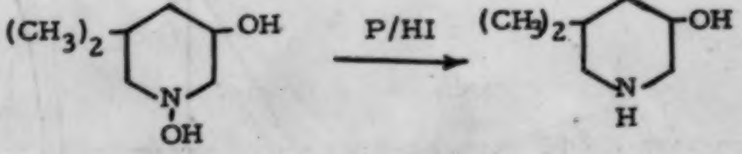
hydroxylamines. Oxidation of the N-hydroxypyrazole dimer (115) with iodine yielded a compound (252) for which preliminary electron spin resonance studies suggest biradical character (Freeman, 1973).



(115) (252)

(G) Reduction:

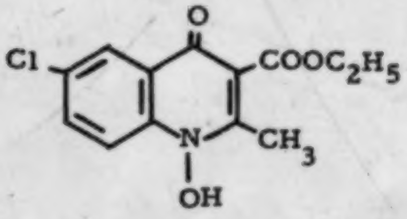
The N-hydroxy function as well as its O-substituted derivatives can be reduced by chemical reagents or by catalytic hydrogenation. Zinc and acetic acid is used very frequently for this purpose. N-Hydroxypyrazoles (Freeman and Gannon, 1969), N-hydroxyimidazoles (Busch, 1931), N-hydroxyindole (Loudon and Wellings, 1960) and N-hydroxypyrroles (Blaise, 1914; Blatt, 1934) were reduced to the corresponding amines by the use of this reagent. Phosphorous and hydroiodic acid were also used for the reduction of 1-hydroxybenzotriazole (Brady and Reynold, 1928) and 1,5-dihydroxy-3,3-dimethyl-piperidine (35) (Brown et al, 1959).



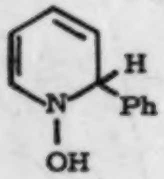
(35) (253)

1-Hydroxyphenmetrazine (12) is said to reduce quantitatively to phenmetrazine (11) by means of titanous chloride or lithium aluminum hydride (Beckett and Salami, 1972). The latter reducing agent was also used for the reduction of some substituted 1-hydroxyimidazole derivatives (Volkamer and Zimmermann, 1969). Other chemical reagents which have been used for the reduction of cyclic hydroxylamines include sodium hydrosulfite (Wright, 1964), tin and hydrochloric acid (Curtius and Mayer, 1907), tin chloride and hydrochloric acid (Minisci *et al*, 1963) and dimethylformamide (Taylor and Garcia, 1964).

The N-hydroxy function is, in most cases, susceptible to catalytic hydrogenation. N-Hydroxybenzimidazoles (Takahashi and Kano, 1963; Minisci *et al*, 1963) and N-hydroxyimidazole (Volkamer *et al*, 1967) were readily hydrogenated over suitable catalysts. In contrast, hydrogenation of the N-hydroxy compound (254) over Pd-C replaced only the chlorine atom with hydrogen without affecting the N-hydroxy function (Loudon and Wellings, 1960). Also, controlled catalytic hydrogenation of 1-hydroxy-2-phenyl-1,2-dihydropyridine (255) over Pd-C resulted only in the reduction of the pyridine ring giving 1-hydroxy-2-phenylpiperidine (Kato and Yamanaka, 1965).

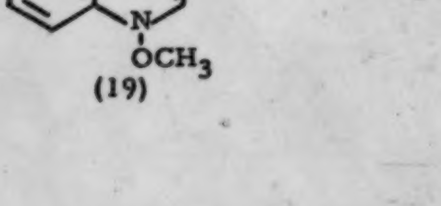


(254)

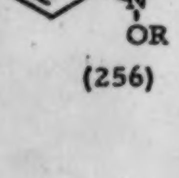


(255)

Reduction of cyclic N-alkoxy compounds generally results in elimination of the N-alkoxy function. The N-methoxy compound (19) was successfully hydrogenated over Pd-C or reduced with lithium aluminum hydride to the corresponding amine (Morimoto and Oshio, 1965). Also, the N-alkoxy groups in (256) were eliminated by catalytic hydrogenation but the rate of elimination was slower than the rate of



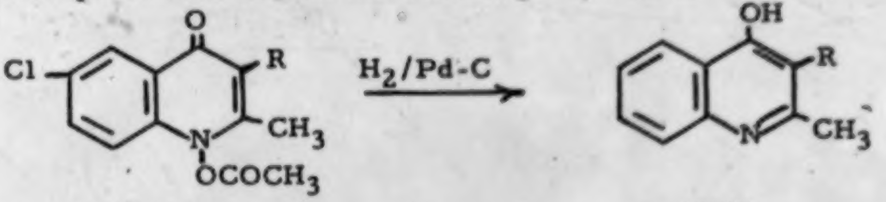
(19)



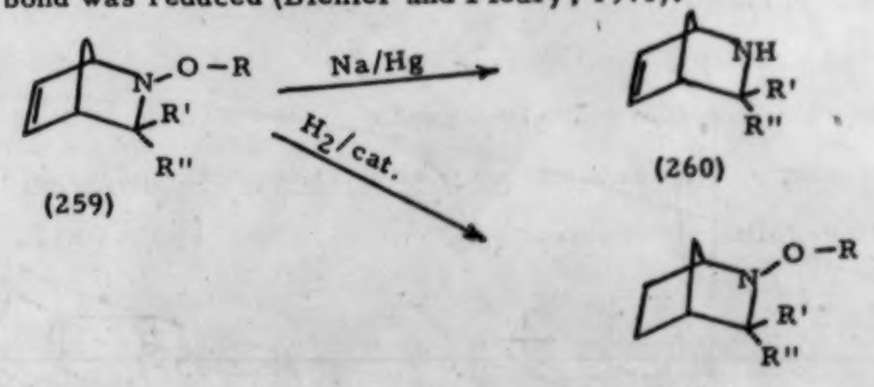
(256)

deoxygenation of the parent N-hydroxy compound (Takahashi and Kano, 1964). In certain cases, however, reduction does not affect the N-alkoxy function. For example, 1-methoxy-2-indole carboxylic acid was reduced with lithium aluminum hydride to yield 1-methoxy-2-hydroxymethylindole and 1-methoxy-2-formylindole; the N-methoxy function was not eliminated (Kawana et al, 1965).

Hydrogenation of acetates of structure (257) over Pd-C caused replacement of both the acetate group and the chlorine atom by hydrogen (Loudon and Wellings, 1960). Sodium-amalgam also reduced the benzoate and sulfonate derivatives of 2-azanorbornenes (259) to (260), but when catalytic hydrogenation was carried out, only the double bond was reduced (Biehler and Fleury, 1971).



(257) (258)

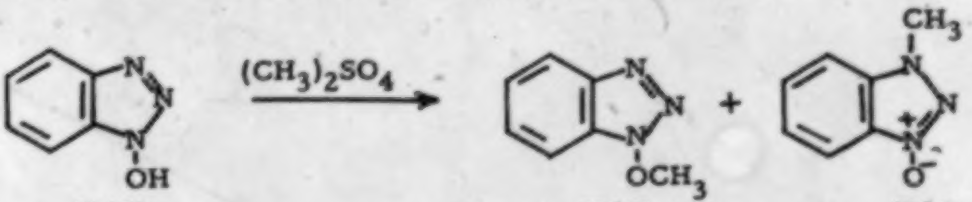


(259) (260) (261)

(H) Alkylation Reactions:

Many N-hydroxy compounds are sufficiently acidic to be O-methylated with diazomethane (Hayashi et al, 1960; Baxter and Swan, 1967; Acheson et al, 1968). Dimethyl sulfate (Kliegel and

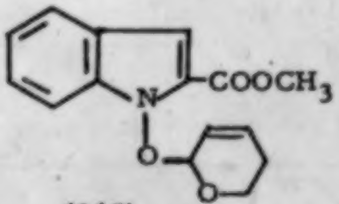
Fehrle, 1914; Brady and Reynolds, 1928; Taylor and Garcia, 1964) and alkyl halides (Curtius and Mayer, 1907; Brady and Day, 1923; Takahashi and Kano, 1964) are used more frequently for this purpose. 1-Hydroxybenzotriazole (146) reacted with dimethyl sulfate to give a mixture of O-methyl (262) and N-methyl (263) derivatives, the ratio of which was found to be alkali-dependent (Brady and Reynolds, 1931; Brady and Jakobovits, 1950). In the absence of alkali and solvent,



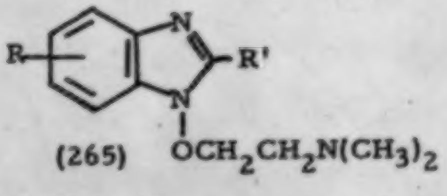
(146) (262) (264)

(146a) was converted only to the N-methyl compound (264), while a better yield of the O-methyl derivative (263) was obtained when the silver salt of (146) was methylated with methyl iodide (Brady and Reynolds, 1928).

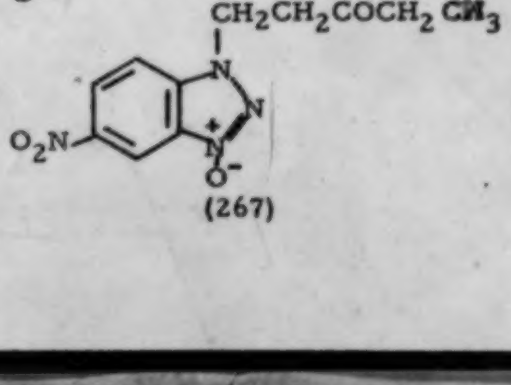
2,3-Dihydropyran reacted with methyl 1-hydroxy-2-indolecarboxylate to yield (265) (Kawana et al, 1965). Similarly, dimethylaminoethyl chloride gave the 1-alkoxy derivative (266) when it reacted with 1-hydroxybenzimidazole in the presence of sodium hydride and dimethylformamide (CIBA, 1966). In contrast, the reaction of 6-nitro-



(265)



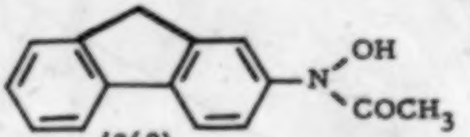
(265)



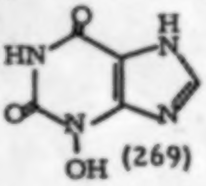
(267)

1-hydroxybenzotriazole with 1-chlorobutan-3-one yielded only the N-substituted product (267) (Shine et al, 1963).

Metabolic O-methylation of some carcinogenic hydroxylamines such as N-acetyl-N-2-fluorenylhydroxylamine (268) (Lotlikar, 1968) and hydroxamic acids such as 3-hydroxyxanthine (269) (Stöhrer, 1972) was performed in vitro using enzyme systems from rat liver or kidney. The methyl donor is S-adenosylmethionine (SAM); cysteine is sometimes required but divalent cations do not stimulate this reaction which appeared to be specific for N-hydroxy compounds (Weisburger and Weisburger, 1973). Both the O-methyl derivatives (268, OCH_3 for OH) and (269, OCH_3 for OH) were also synthesized, but it is not known yet whether these can react with nucleophilic compounds as the corresponding esters (acetates, glucuronides and sulfonates) do. Accordingly, the biological significance of this reaction is not yet established.

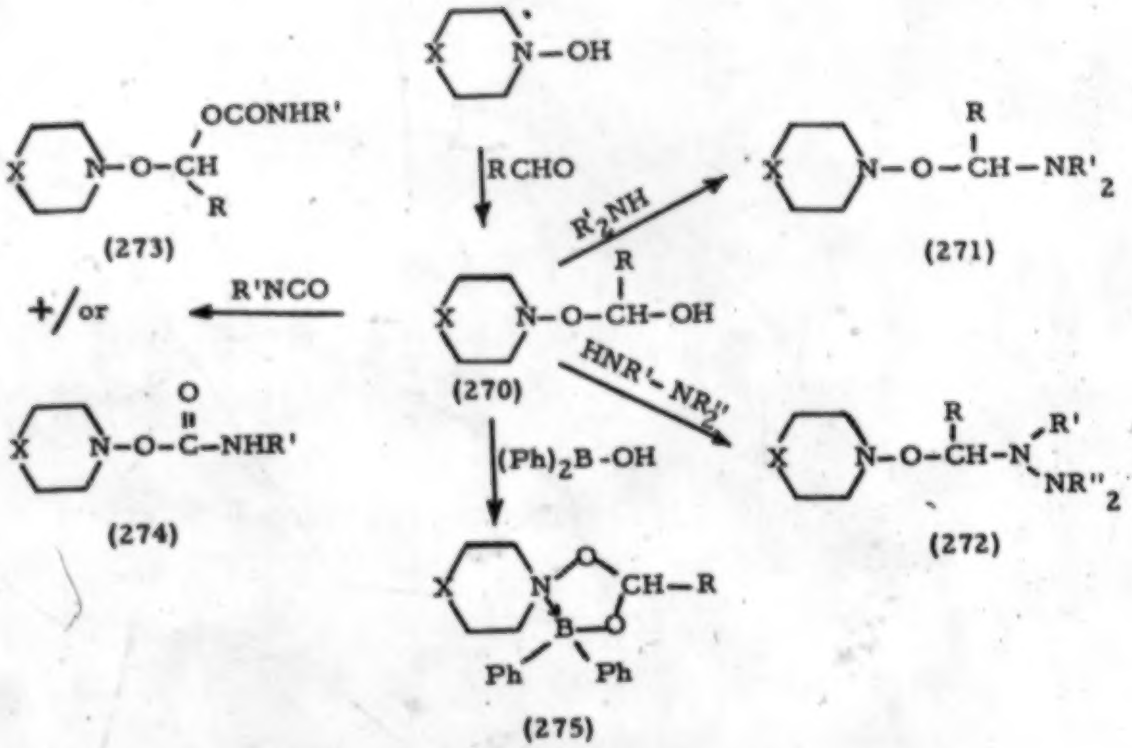


(268)

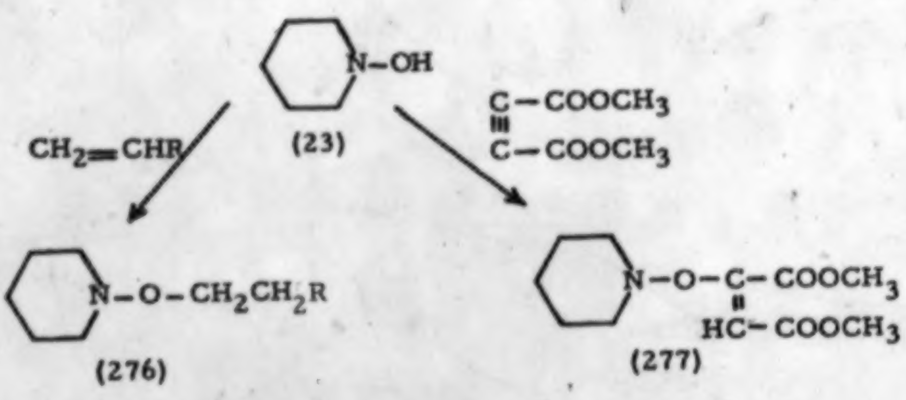


(269)

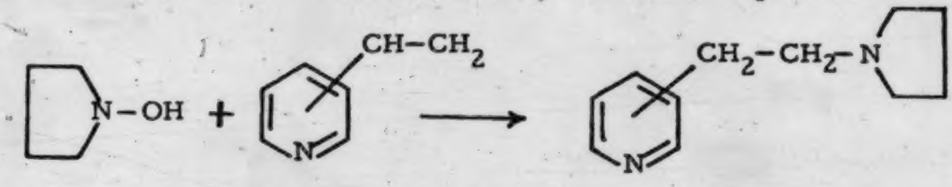
Several aldehydes react with cyclic N-hydroxy compounds to give O-semiacetals (270) which are converted to the so-called "mixed N,O-acetals" (271) and (272) when reacted with amines or hydrazines (Zinner and Kliegel, 1966). Treatment of the semiacetal (270) with arylisocyanates yielded (274) or a mixture of (274) and (273) (Zinner et al, 1965) while reaction of (270) with diphenyl boric acid gave 5-boro-1,2,4-dioxazole derivatives (275) (Zinner and Moll, 1966; Zinner and Kliegel, 1966).


N–OH
X
RCHO
R'₂NH
HNR'–NR''₂
R'NCO
(Ph)₂B-OH
+/or
N–O–CH(OH)R
(270)
N–O–CH(R)–NR'₂
(271)
N–O–CH(R)–N(R')–NR''₂
(272)
N–O–CH(OCONHR')R
(273)
N–O–C(=O)–NHR'
(274)
CH–R
Ph
Ph
(275)

1-Hydroxypiperidine has been successfully condensed in a Michael-type reaction with various electron deficient alkenes ($RCH{=}CH_2$; $R{=}COCH_3$, COOR, CN) to produce adducts (276) (Zinner et al, 1965). The N-hydroxy group also added across the triple bond of acetylene dicarboxylic acid esters giving the adduct (277) (Winterfeldt and Krohn, 1969). On the other hand, the reaction of 1-hydroxypyrrolidine (4)

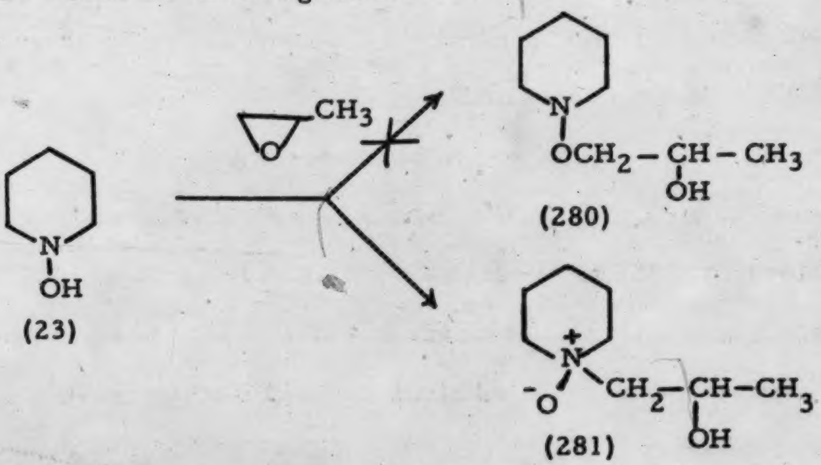

N–OH
(23)
CH₂=CHR
C–COOCH₃
C–COOCH₃
N–O–CH₂CH₂R
(276)
N–O–C–COOCH₃
HC–COOCH₃
(277)

with 2- or 4-vinylpyridines (278) resulted in the loss of the oxygen atom and gave pyridylethylpyrrolidine (279) (Thesing and Sirrenberg, 1959). This "abnormal" Michael reaction was found to proceed in the absence as well as in the presence of acidic (HOAc) or basic (Triton B) catalysts (Paquette, 1962).



(4) (278) (279)

Treatment of N-hydroxypiperidine (23) with propylene oxide was said to proceed via O-alkylation to give 1-piperidinoxy-2-propanol (280) (Zinner and Ritter, 1962). This report was discounted by Cannon et al (1969) who showed that the product was, in fact, the amine oxide (281). Based on this, the products obtained by the reaction of other N-hydroxy compounds with alkylene oxides (Zinner et al, 1965) would be worth a reinvestigation.

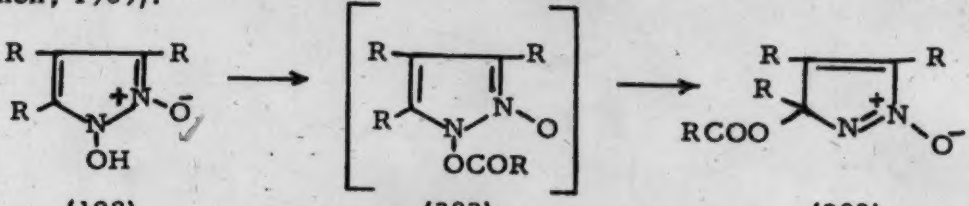


(23) (280) (281)

(I) Acylation and Sulfonation Reactions:

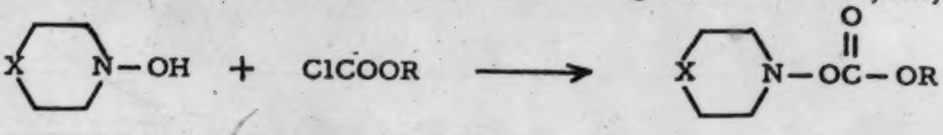
Acetyl, benzoyl and sulfonyl chlorides react readily with cyclic N-hydroxy compounds to form acetate, benzoate and sulfonate derivatives. Acetic anhydride, benzoic anhydride as well as ketene are also used for this purpose. Alternatively, cyclic acetoxy and benzoyloxy derivatives are obtained by the action of acetyl or benzoyl peroxide on the corresponding cyclic amines or by condensation reactions in which the acyloxy function is already present in one of the reacting components.

1-Acetyloxypiperidine was prepared by the action of acetyl chloride, acetic anhydride or ketene on 1-hydroxypiperidine (Zinner, 1957a). Similarly, treatment with benzoyl chloride yielded 1-benzoyloxypiperidine. Both these acyloxy derivatives were also prepared by reacting piperidine with the corresponding acyl peroxide (Gambarian and Kazaryan, 1933; Sammes, 1965; Zinner, 1958). Similar preparations of N-acetoxy and N-benzoyloxy derivatives of morpholine, indoles, imidazoles, pyrazoles, benzimidazoles and benzotriazoles are known; examples of these compounds are presented in table 1. There are cases, however, where dehydrated or rearranged products were obtained. For example, acetylation of 1-hydroxy-2-phenyl-1,2-dihydropyridine by heating with acetic anhydride gave only the dehydrated product, 2-phenylpyridine (Kato and Yamanaka, 1965). Benzoylation of the same compound at low temperature was successful and yielded the O-benzoyl derivative. With 1-hydroxypyrazole 2-oxides (198), the acetyl and benzoyl derivatives (282) formed initially then rearranged to (283). In the absence of the N-oxide function, however, O-benzoyl derivatives could be isolated (Freeman and Gannon, 1969).

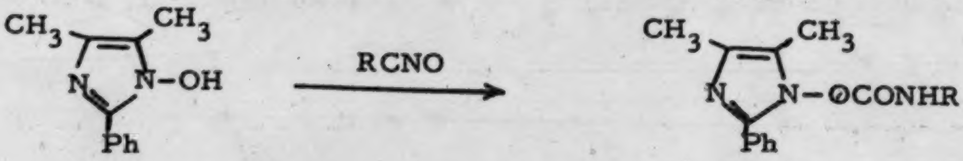


(198) (282) (283)

The N-hydroxycarboxylic acid esters (285) were prepared by the action of alkyl chloroformates on the N-hydroxy compounds (284) (Zinner, 1957; Zinner and Kliegel, 1966). Isocyanate derivatives also react with cyclic hydroxylamines to give N-carbamoyloxy derivatives (287) (Zinner and Kliegel, 1966; Akagane *et al*, 1969).

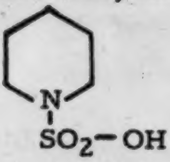


(284) X=CH$_2$ or O (285)



(286) (287)

Sulfonate derivatives of N-hydroxy compounds are less stable than the corresponding acetates or benzoates and only a few O-sulfonates have been isolated. Zinner (1957, 1958, 1958a) described the formation of piperidine N-sulfonic acid (288) and piperidine N-oxysulfinic acid ethyl ester (289) by the interaction of 1-hydroxypiperidine with sulfur dioxide and chlorosulfinic ester respectively. The stable tosylate (290) was also isolated (Freeman *et al*, 1959).



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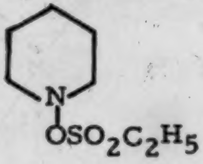

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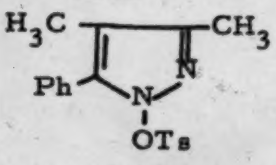
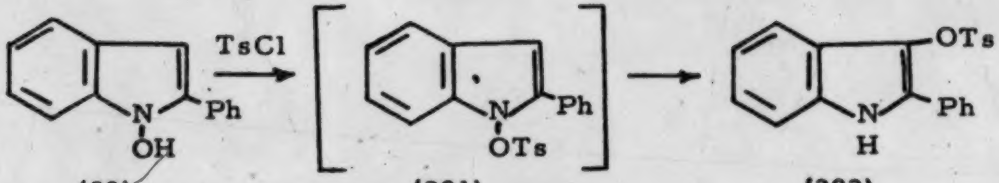


(290)

On the other hand, attempts to prepare the O-sulfonate derivative (291) by reacting (83) with p-toluenesulfonyl chloride gave a rearrangement product which was formulated as (292) (Sundberg, 1965). Similar rearrangements were also observed (Tanida, 1959; Gassman and Hartman, 1972) during attempted sulfonation of other N-hydroxy



(83) (291) (292)

compounds.

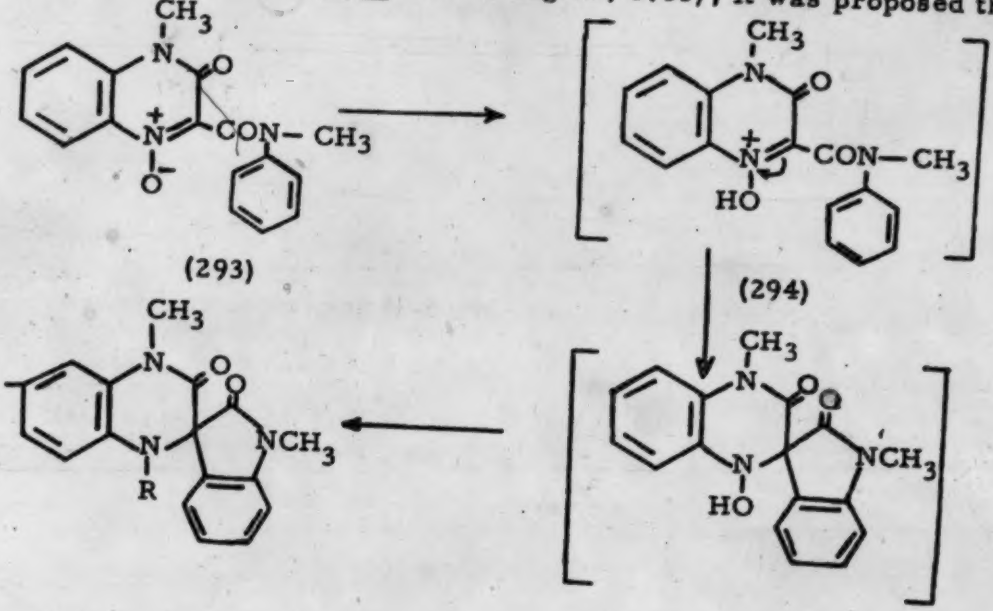
The possibility of employing N-acyloxy derivatives of cyclic hydroxylamine as acylating agents was studied by Sammes (1965). N-Benzoyloxypiperidine was found to react with benzylamine and with ethyl aminoacetate to give N-benzylbenzamide and hippuric acid respectively. N-acetoxypiperidine was also shown to be a reactive acylating agent. Beaumont et al (1965) as well as Young and Handford (1967) have demonstrated the usefulness of these esters and other esters of N-hydroxypiperidine in peptide synthesis and as selective acylating agents.

(J) Reactions with Nucleophilic Reagents:

The reactions of arylhydroxylamines and hydroxamic acids with different nucleophilic reagents including tissue nucleophiles (amino acids, proteins and nucleic acids) have been studied in great detail. However, only few of these reactions have been attempted with cyclic hydroxylamines or their alkyl, acyl or sulfonyl derivatives. The importance of these studies is to provide information on any interactions which might occur between cellular macromolecules and N-hydroxy compounds once they are metabolically formed in the body.

Clark-Lewis and Katekar (1959) found that ethanolic hydrogen chloride converted the N-oxide (293) to the spiro-quinoxaline derivative (296, R=H). When hydrogen chloride was replaced with acetyl chloride, the 1-acetyl derivative (296, R=$COCH_3$) was formed.

In view of the work on the interaction of phenylhydroxylamine with chloride ions (Heller et al, 1951; Ingold, 1953), it was proposed that



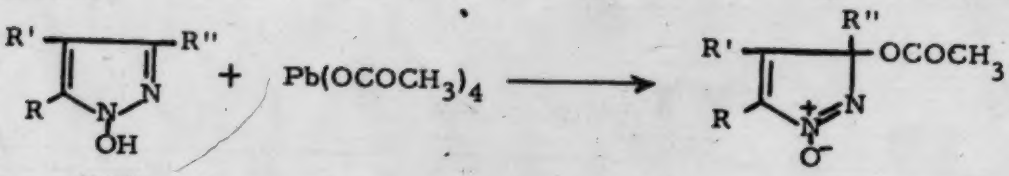
(293)

(294)

(296)

(295)

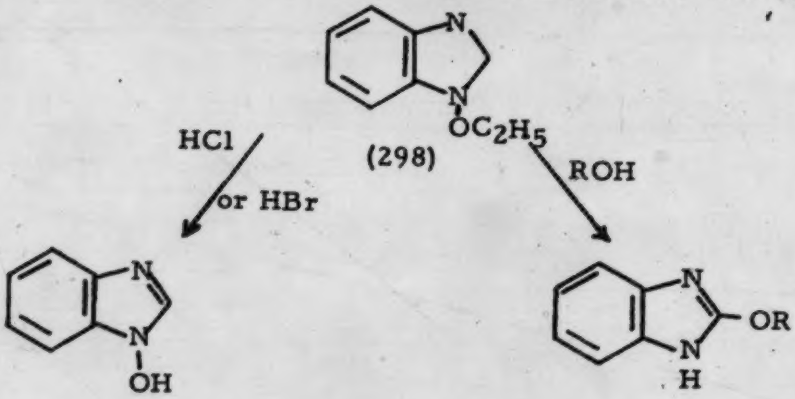
the conversion of (293) to (296) proceeded via an N-hydroxy intermediate (295). Attempts by Habib and Rees (1962) to prepare the latter compound failed, although, as described earlier in this introduction, they were able to prepare the structurally related N-hydroxypyrazine (208) by the action of ethanolic hydrogen chloride on 3,4-dihydro-4-methyl-2-(N-methyl-N-phenylcarbamyl)-3-oxopyrazine 1-oxide(207). No chlorinated derivatives were isolated from this reaction. Similarly, refluxing a crude product containing 1-hydroxyindole-2-carboxylic acid with methanolic hydrogen chloride results in the formation of its methyl ester without elimination of the N-hydroxy function (Baxter and Swan, 1967). Also, treatment of the 1-hydroxypyrazole (296) with lead tetracetate yielded the acetate derivative (297) in which the N-O bond remained intact (Freeman and Gannon, 1966).



(296)

(297)

Heating 1-ethoxybenzimidazole (298) with hydrochloric or hydrobromic acids in a sealed tube, caused cleavage of the C-O bond of the ethoxy group giving N-hydroxyimidazole (276) (Takahashi and Kano, 1964). On the other hand, the 2-alkoxy derivatives (299) were obtained when (298) was heated with sodium alkoxide. The same

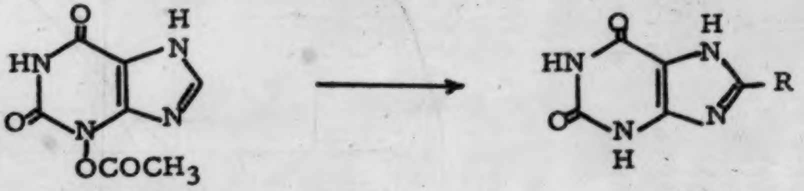


(226)

(299)

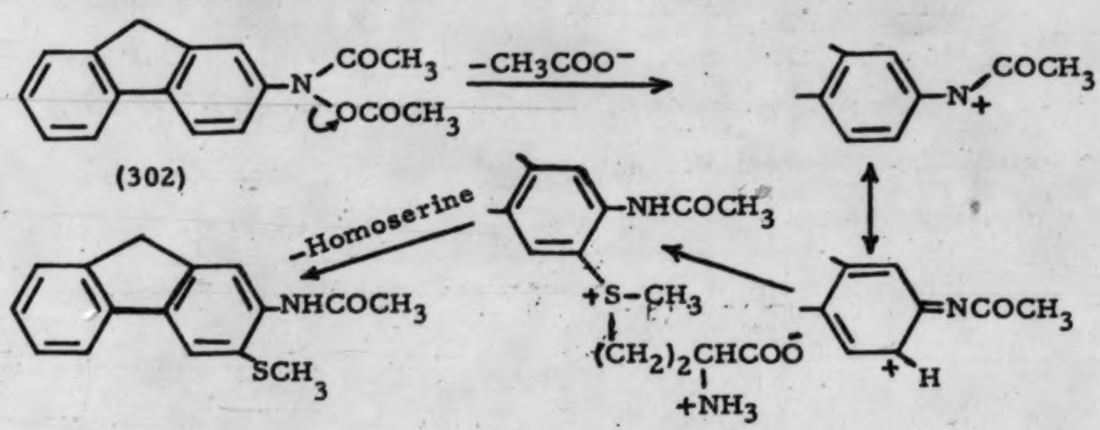
N-ethoxy compound (298) reacted with nucleophilic reagents such as hydrazine hydrate and sodium hydrogen sulfite to give 2-hydrazinobenzimidazole and sodium 2-benzimidazolesulfonate respectively, but it did not react with potassium cyanide except at elevated temperature to give a poor yield of 2-benzimidazole carbamic acid. In these reactions, it was assumed that a nucleophilic reagent attacked the electron deficient 2-position of 1-alkoxybenzimidazoles, then elimination of alcohol occurred to give 2-substituted benzimidazoles (Takahashi and Kano, 1964).

Biochemically, glucuronide, sulfonate and acetate esters were found to be more reactive with tissue nucleophiles than their parent N-hydroxy compounds. Although enzymic O-acetylation of foreign compounds containing hydroxyl groups could not be demonstrated, O-acetate derivatives such as (300) and (302) have been used as model derivatives of their respective potential glucuronide or sulfonate conjugates. Compound (300) reacted _in_ _vitro_ with chloride ion or methionine to give 8-chloroxanthine (201, R=Cl) and 8-methylmercaptoxanthine (301, R=SCH_3) which are identical to two urinary



(300) (301)

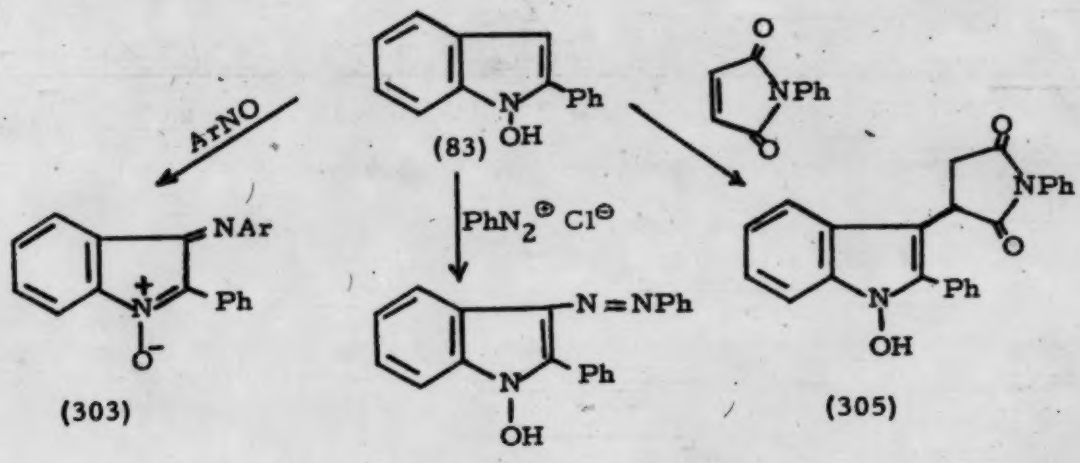
metabolites of 3-hydroxyxanthine (Stöhrer and Brown, 1970). This reaction with methionine is reminiscent of the well studied (Lotlikar _et_ _al_, 1966; Miller _et_ _al_, 1966; Irving, 1970) interaction of the carcinogenic model compound N-acetoxy-N-acetyl-2-aminofluorene (302) with tissue nucleophiles. A proposed mechanism of the interaction of (302) with methionine is shown in scheme 1 (Miller and Miller, 1969).



Scheme 1

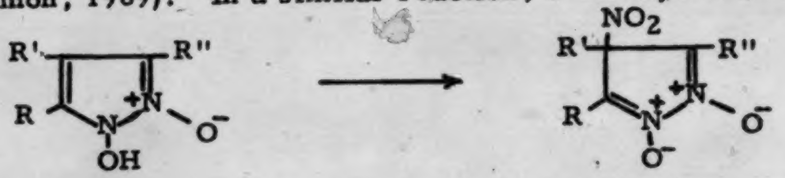
(K) Reactions with Electrophilic Reagents:

The reactions of 1-hydroxy-2-phenylindole (83) with a number of electrophilic reagents were studied by Colonna and his co-workers. Treatment of (83) with aromatic nitroso compounds gave 2-phenyl-3-aryliminoindole 1-oxide (303) (Colonna and Bruni, 1967, 1967a). An adduct of 1-hydroxy-2-phenyl-3-(phenylazo)indole (304) with (83) was formed when the latter was treated with phenyldiazonium chloride (Colonna and Bruni, 1964). The same N-hydroxy compound (83) reacted with some dienophiles such as N-phenylmaleimide to yield 1-hydroxy-2-phenyl-3-(N-phenylsuccinimidyl)indole (305) (Colonna and Monti, 1962).



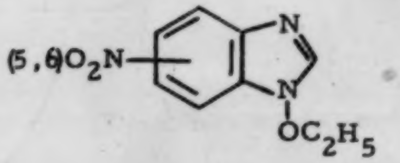
(83) (303) (304) (305)

1-Hydroxypyrazole 2-oxides (198) reacted with nitrous acid in an electrophilic substitution reaction followed by oxidation with the excess acid to yield nitropyrazolenine 1,2-dioxides (306) (Freeman and Gannon, 1969). In a similar reaction, 1-ethoxybenzimidazole



(198) (306)

gave a mononitro derivative (307) when treated with a mixture of fuming nitric acid and sulfuric acid at room temperature and a dinitro derivative (308) on heating (Takahashi and Kano, 1964).



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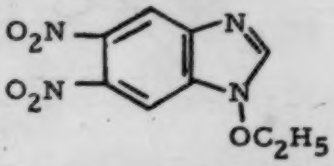
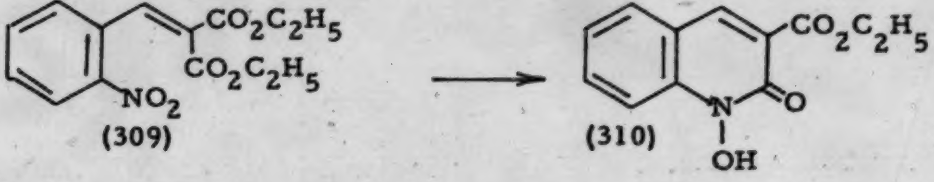


(308)

SCOPE OF THE PRESENT INVESTIGATION.

The preparation of some novel cyclic N-hydroxy compounds was the primary objective of the research described in this thesis. Assumming that these compounds could be obtained, a study of some of their chemical and pharmacological properties was also desirable in order to help understand the recent flow of biochemical studies in this area. This problem was approached by attempting the reductive cyclization of some aromatic nitro compounds which have a side chain with a carbonyl group suitably orientated with respect to the nitro group. Coutts and his co-workers (Coutts and Wibberley, 1963; Coutts, Noble and Wibberley, 1964; Coutts, Peel and Smith, 1965; Coutts, Barton and Smith, 1966; Coutts and Hindmarsh, 1966; Coutts and Smith, 1967). have shown that this type of compound can be reductively cyclized by sodium borohydride and palladium-charcoal and although under normal conditions, aromatic nitro compounds are normally reduced to amines, o-nitro esters e.g. (309), gave good yields of cyclic hydroxamic acids (310). This might be the most reliable method for the reductive cycli-



(309)

(310)

zation of a nitro ester to a hydroxamic acid (Bapat et al, 1969). The formation of cyclic N-oxy and N-hydroxy compounds by using the same reduction system has also been described (Coutts and Wibberley, 1963).

The reduction of 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (98), compounds which possess a lactam carbonyl group, was investigated by Coutts and Edwards (1966). These authors claimed that these compounds cyclized to N-hydroxypyrazoloquinoline derivatives (99) when reduced with cyclohexene and palladium-charcoal; the catalyzed sodium borohydride reductions were less successful. This work was reinvestigated in this present study and this has shown that the products were not N-hydroxy compounds. The method was modified and other reduction systems were also used until some cyclic N-hydroxyindolines were successfully prepared. These were characterized and a study of their chemical reactivity was undertaken. The mass spectra of these compounds as well as the mass spectra of some pyrazolone derivatives were also recorded and examined. During these reductions, other compounds including spiro-(tetrahydroquinoline)pyrazolones were also obtained and characterized.

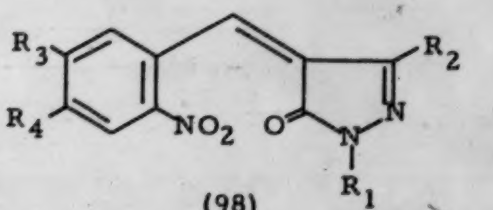
These results suggested a reinvestigation of the reductions of 4-(2-nitrophenylthio)-2-pyrazolin-5-ones (400) which was claimed (Pound, 1970) to have yielded N-hydroxybenzothiazines (402). The same products described by Pound (1970) were isolated but were also found not to be N-hydroxy compounds.

DISCUSSION

PART 1: REDUCTION OF SOME 4-(2-NITROBENZYLIDENE)-2-PYRAZOLIN-5-ONES

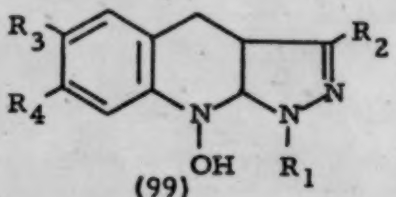
Introduction:

The value of using sodium borohydride/palladium-charcoal for the reductive cyclization of some aromatic nitro compounds which possessed an acidic or an ester group in a position capable of undergoing cyclization has already been discussed. Coutts and Edwards (1966) tried this method, among others, to reduce aromatic systems which possessed suitably orientated nitro and lactam carbonyl groups in order to obtain some novel cyclic N-oxides or N-hydroxy compounds. They prepared a series of 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (98) and reduced them using several methods which were known to yield N-oxides or N-hydroxy compounds in certain instances. The cyclic N-hydroxy compounds, 9-hydroxypyrazolo[3,4-b] quinolines (99) were reported to be among the reduction products obtained (Coutts and Edwards, 1966).



(98)

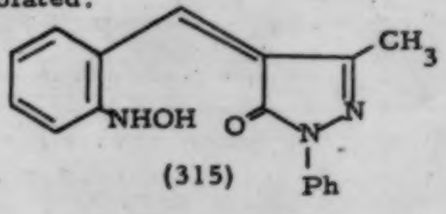
	R_1	R_2	R_3	R_4
a;	C_6H_5	CH_3	H	H
b;	C_6H_5	C_6H_5	H	H
c;	C_6H_5	CH_3	Cl	H
d;	C_6H_5	CH_3	OCH_3	OCH_3



(99)

	R_1	R_2	R_3	R_4
e;	C_6H_5	CH_3	$O-CH_2-O$	
f;	H	CH_3	H	H
g;	$COCH_3$	CH_3	H	H

One of these reduction products (99a) was previously claimed (Narang et al, 1934) to be a product of the reduction of (98a) by either aluminum amalgum, zinc dust and acetic acid or alcoholic hydrochloric acid. Narang et al (1934) suggested that this reduction proceeded through the hydroxylamine compound (315) which they also claimed to have isolated.

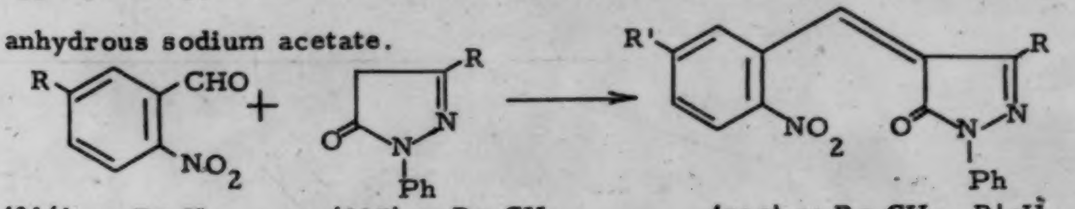


(315)

As this present investigation was aimed mainly at the preparation of some cyclic N-hydroxy compounds to study their chemical behavior and evaluate their pharmacological activity, this reported work was reinvestigated first.

Preparation of some 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (318a-c).

The three 2-nitrobenzylidene derivatives chosen for this investigation were: 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one(318a), 4-(2-nitrobenzylidene)-1,3-diphenyl-2-pyrazolin-5-one(318b) and 4-(5-chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one(318c). These were prepared by a known method (Coutts and Edwards, 1966) which involved heating of o-nitrobenzaldehyde (316a) or 3-chloro-6-nitrobenzaldehyde (316b) with the appropriate pyrazolone derivatives (317) in acetic anhydride containing anhydrous sodium acetate.



(316) a; R = H

b; R = Cl

(317) a; R = CH_3

b; R = C_6H_5

(318) a; R = CH_3, R' = H

b; R = C_6H_5, R' = H

c; R = CH_3, R' = Cl

One of the pyrazolones required for this synthesis, 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) was available commercially and the other, 1,3-diphenyl-2-pyrazolin-5-one (317b) was prepared by the interaction of ethylbenzoyl acetate with phenylhydrazine.

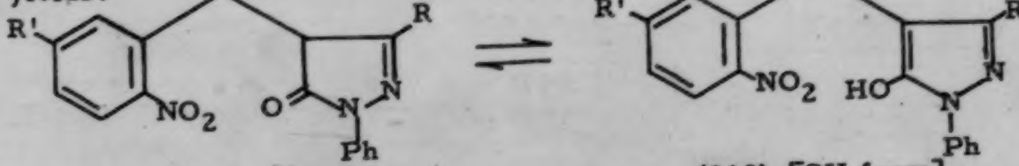
Reduction of the O-nitrobenzylidene derivatives (318a-c) with sodium borohydride and palladium-charcoal.

Method (A): Reductions in methanol.

Initially, the reduction method used by Coutts and Edward, 1966 was followed except that methanol was used as solvent instead of an ethanol-methanol mixture. The same products were isolated, i.e. the major amphoteric compounds which were claimed to be the 9-hydroxypyrazolo[3,4-b]quinolines (99 a-c), and the minor ones which Coutts and Edwards (1966) left unidentified. However, due to some difficulties in obtaining pure analytical samples of some of these derivatives, a modification in the reduction procedure was sought.

Method (B): Reductions in 10% sodium hydroxide solution.

The O-nitrobenzylidene derivatives (318a-c) were first reduced by means of sodium borohydride in dioxane solution. This resulted only in the reduction of the benzylidene double bond and 4-(2-nitrobenzyl)-2-pyrazolin-5-ones (319) were isolated in excellent yields.



(319) [CH form]

(319) [OH form]

a; $R = CH_3$, $R' = H$

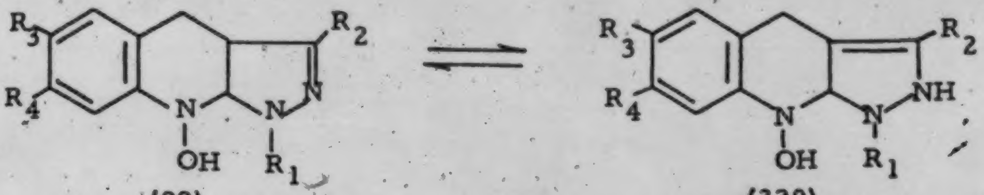
b; $R = Ph$, $R' = H$

c; $R = CH_3$, $R' = Cl$

Once the benzylidene double bond is reduced, these pyrazolones (319) become soluble in dilute alkali due to their ability to enolize. In view of this, catalytic (10% Pd-C) sodium borohydride reductions of the pyrazolones (319) were carried out in dilute sodium hydroxide solution. Acidification of the filtrate from the reaction with dilute acetic acid caused precipitation of the reduced products.

By using this modified procedure, only one type of product was isolated. Although melting points were considerably higher than those of the amphoteric products obtained by reduction in methanol, they had the same solubility characteristics and the same i.r. spectra as those reported for the compounds prepared by Coutts and Edwards (1966).

Narang et al (1934) concluded that the 9-hydroxypyrazoloquinoline (99 a) was the reduction product of the pyrazolone (98 a) from a correct elemental analysis, and because the product was found to be soluble in both acids and alkalies. When Coutts and Edwards (1966) reduced the same compound (98 a) and derivatives (98 b-g), they concluded that in addition to the correct elemental analyses and solubility characteristics, the i.r. spectra of the reduction products were also in agreement with structure (99). The i.r. spectra(solid), showed broad absorption in the 2100-3500 cm^{-1} range with maxima between 2850 and 3090 cm^{-1} which was attributed to the N-OH function. Also a C=O absorption band was apparently absent from these spectra. Similar spectra were obtained when the pure samples obtained in the present investigation were examined as solids (KBr or nujol), but two additional medium size absorption maxima were located at ~3200 and ~3350 cm^{-1}. This was initially considered to be due to the ability of such compounds (99) to tautomerise (320) and thus display an NH absorption band in addition to that of the N-OH function. However, the



(99) (320)

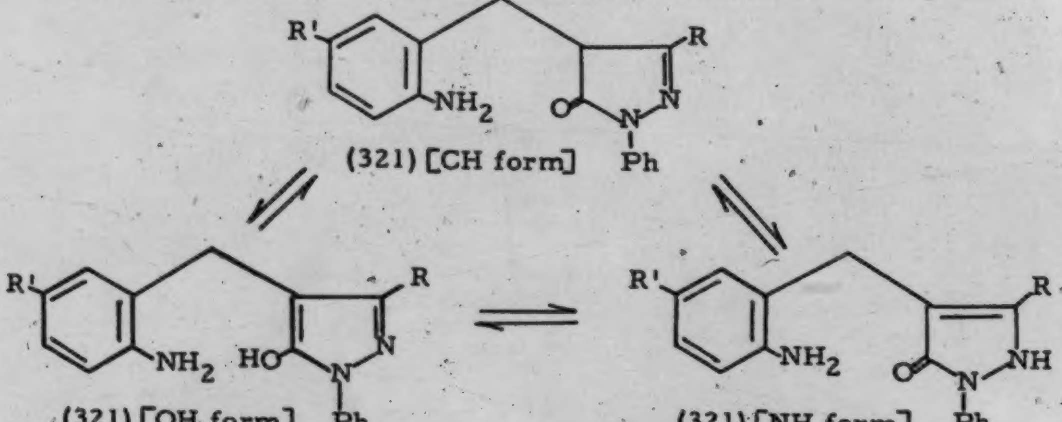
plausibility of N-hydroxy structures (99) being formed at all, was seriously questioned when the n.m.r. and mass spectra of these reduction products were recorded and interpreted.

The n.m.r. spectrum (in DMSO-d_6) of the amphoteric product obtained by reduction of the pyrazolone (319a), displayed two signals at $\delta 2.1$ (CH_3) and at $\delta 3.43$ (CH_2) and an aromatic multiplet (12 protons). When the sample was shaken with deuterium oxide, three protons within the aromatic area were found to be D-exchangeable. Three D-exchangeable protons, with almost the same chemical shifts were also found in the n.m.r. spectrum of the reduction product of the phenyl analog (319b). These three protons shifted upfield when $CDCl_3$ was the solvent used; in this solvent they appeared as a broad peak around $\delta 6.0$. The presence of three D-exchangeable protons in each of these spectra does not agree with the proposed structures (99 $\rightleftharpoons$ 320) in which only one or two such protons would be expected.

The mass spectra of the reduction products (Fig. 1) displayed molecular ions consistent with the molecular formulae of the proposed structures (99 a,b). However, the mode of fragmentation of these compounds under electron impact (Scheme 2) revealed that intact pyrazolone ring (ion b) was still present in the molecules.

The expulsion of an oxygen atom or an $\dot{O}H$ radical which might be expected from a cyclic N-hydroxy structure (99) was not demonstrated. Both of these losses were displayed by some authentic N-hydroxy compounds prepared and described later in this thesis. Instead, the expulsion of a molecule of water (to form ion d or e) followed by the loss of a hydrogen atom (presumably to form the stable pyrazoloquinoline f) was observed (see Scheme 2). The absence of an $(M-18)^+$ ion in the mass spectrum of the related amine (416), in which the methylene group is replaced with a sulfur atom, suggested that one of the methylene hydrogen atoms is involved in the loss of a water molecule from the molecular ion of (321). This suggestion was also supported by the presence of an $(M-18)^+$ ion in the mass spectrum of the triacetylated derivative (326) (see Scheme 4, p. 94).

At this point, it was concluded that the proposed structures ($99 \rightleftharpoons 320$) for the reduction products in question were not correct. The isomeric amine structure (321) was seen to fit all the previously described data. Such a structure is best written in its three possible



a; R = CH_3, R' = H

b; R = Ph, R' = H

c; R = CH_3, R' = Cl

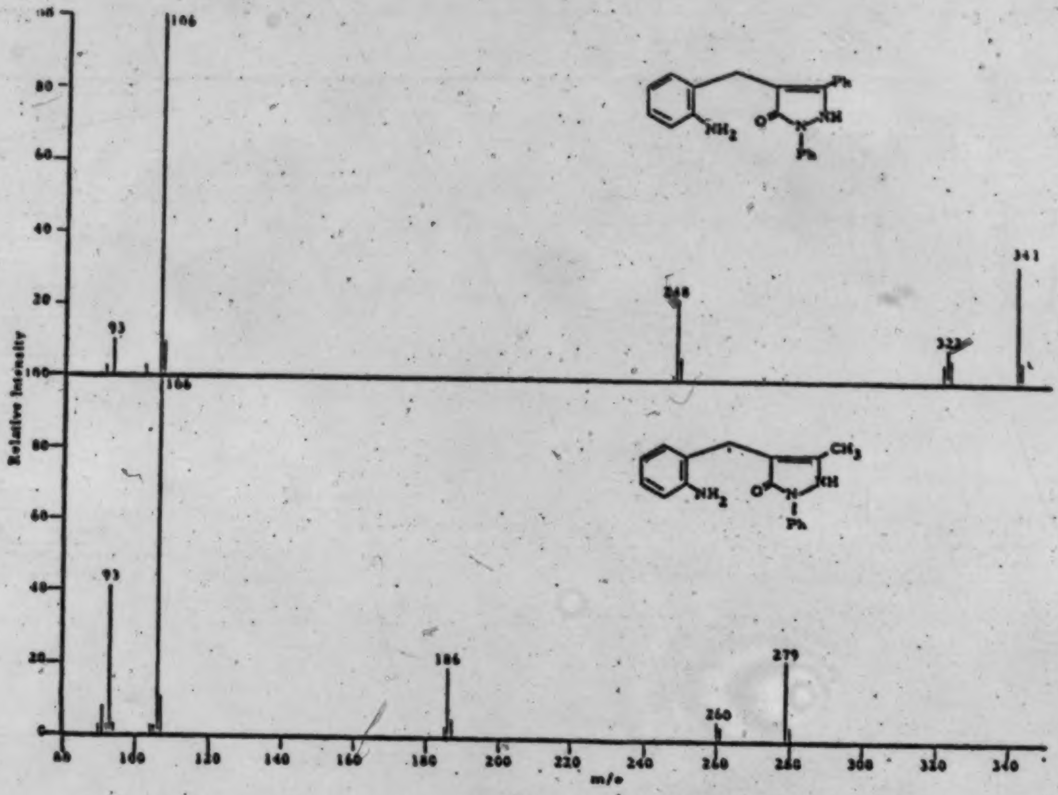
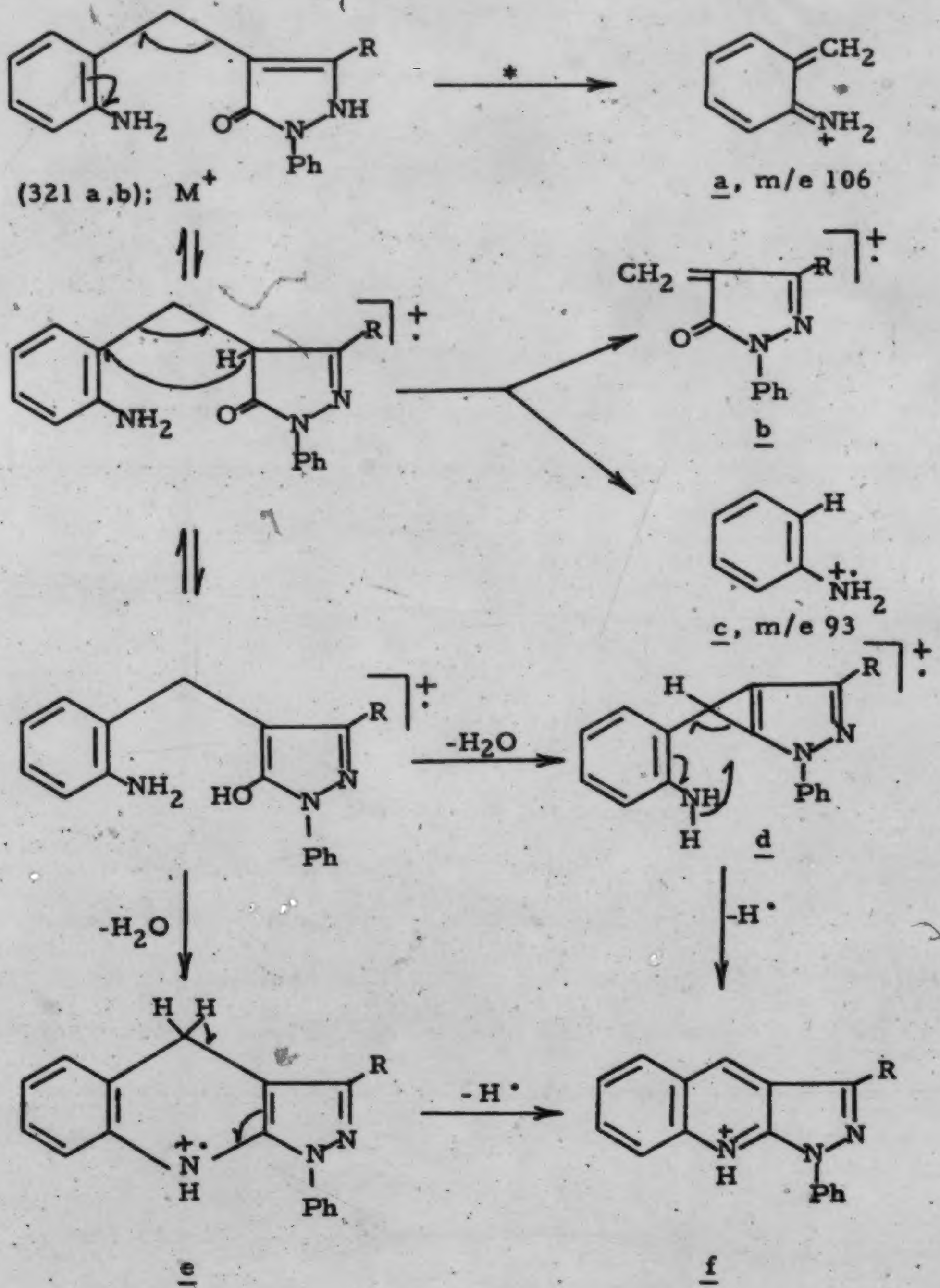


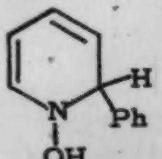
Fig. 1: Portions of the mass spectra of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a) and 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b).

tautomeric forms which can be designated, using the nomenclature of Katritzky and Maine (1964) as the CH, NH or OH forms according to the position of the labile proton.


(321 a,b); M+
a, m/e 106
b
c, m/e 93
d
e
f
-H2O
-H2O
-H•
-H•
*
R
NH2
NH
N
O
HO
Ph
CH2
H

Scheme 2

Two main reasons contributed to the earlier incorrect assignment of structure (99) to the amphoteric reduction products. The first was their solubility in dilute alkali solutions which was believed to be due to the acidity of the N-hydroxy function. It is true that some cyclic hydroxylamines such as (255) (Kato and Yamanaka, 1965) and (7, R=Ph) (Sundberg, 1965) are soluble in alkalies. However, some other related compounds such as (7, R=CH_3) (Acheson et al, 1970) and (322) (Kato and Yamanaka, 1965) are known to be only very weakly acidic and do not dissolve in alkali solutions.



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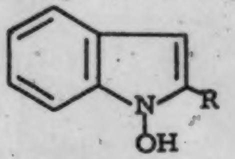

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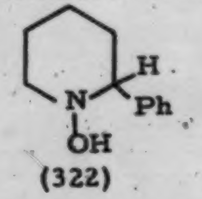
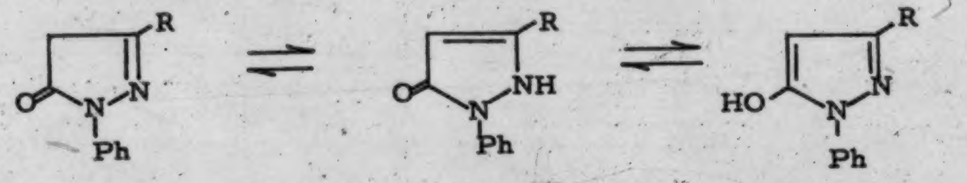


(322)

The second reason which is probably more important, was the fact that C=O absorption was apparently absent from the i.r. spectra of the reduction products when solids were examined. This was taken as an indication that cyclization involving the lactam C=O groups had occurred. It is now revealed that C=O absorption can be demonstrated in both solution and solid spectra of the reduced compounds. Dilute solutions (2%) of the amines (321a,b) in chloroform, gave spectra which displayed a C=O absorption band at 1712 cm^{-1} for (321a) and at 1711 cm^{-1} for (321b). This indicated that the amines existed mainly in the CH form in chloroform (Newman and Pauwels, 1969). These bands completely disappeared when the more polar dimethylsulfoxide was used as a solvent. Instead, another C=O absorption doublet was present at 1660 cm^{-1} (average) for (321a) and at 1654 cm^{-1} (average) for (321b). This shift in the carbonyl absorption is expected when the NH form is present since the pyrazolone ring is comparable to an α,β-unsaturated ketone in this tautomer (Nakanishi, 1962). The multiplicity of these bands and their occurrence at lower frequencies than expected are considered to be due to hydrogen bonding with solvent. The presence of the OH form, in addition to the NH form, in dimethylsulfoxide was indicated mainly by the C=N absorption bands around 1603 cm^{-1}.

A closer look at the i.r. spectra of these amines (321) in the solid form, revealed the presence of a strong absorption band at 1628 cm^{-1} in (321a) and at 1625 cm^{-1} in (321b). The possibility of these bands being due to a C=O absorption was not considered initially and they were assigned to C=N absorption. However, the absence of similar bands in the spectra of intermediate pyrazolones (319) and their presence in those of some amine derivatives e.g. (324) which should be devoid of a C=N double bond, suggested that these bands might be due to a bonded C=O absorption. To examine this possibility, the i.r. spectra of the pyrazolones (317) and (319) were recorded in the solid form. In agreement with some of the earlier reports* (Pelz et al, 1960; Refn, 1961), 3-methyl-2-phenyl-1-pyrazolin-5-one (317a) and 1,3-diphenyl-2-pyrazoline-5-one (317b) were found to exist only in the OH-forms in the solid state. The lack of any C=O



(317)[CH form]　(317)[NH form]　(317)[OH form] absorption confirms the absence of any contribution from the CH or NH-forms. The C=N absorption bands in the spectra were located at 1606 cm^{-1} in (317a) and at 1601 cm^{-1} in (317b). The two 4-(2-nitrobenzyl)-2-pyrazolin-5-ones (319a,b) were also found to exist in OH forms in the solid state. Their spectra displayed broad OH absorption bands between 2400 and 3200 cm^{-1} and C=N absorption was assigned to the bands at 1605 and 1604 for (319a) and (319b) respectively; no other absorption was demonstrated in the 1600-1800 cm^{-1} region.

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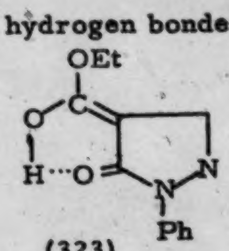
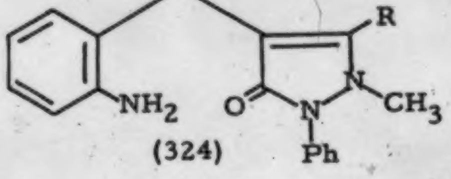
* Katritzky and Maine (1964) considered that, except in special cases, all pyrazolones including (317a) and (317b) exist in the solid state as strongly bonded NH-form which are capable of proton transfer to give the OH-form.

In the spectra of the amines (321), the absorption bands at 1604 for (321a) and 1600 for (321b) could be assigned to the C=N absorption in agreement with the nitro analogs (321a) and (321b). Accordingly, the other strong absorption bands at 1628 and 1625 cm^{-1} in (321a) and (321b) respectively must be due to a bonded C=O absorption. This could be due to the contribution of the NH tautomer in addition to the OH tautomer in the solid state. In the NH tautomer, the C=O absorption is expected to be around 1670 cm^{-1}, but this could be shifted to a lower frequency due to the presence of a strong intermolecular or intramolecular hydrogen bonding. The possibility of the latter was indicated by the presence of the amine absorption maxima at unusually low wave numbers [3200 and 3345 cm^{-1} for (321a) and 3170 and 3350 for (321b)]. A case in which a lactam C=O group was found to absorb at such a low frequency was reported by Newman and Pauwels (1969). In the pyrazolone (323) a band found at 1620 cm^{-1} was assigned to the intramolecularly hydrogen bonded lactam C=O group.



(323)

The assignment of the absorption band around 1625 cm^{-1} in (321) to a $C{=}O$ absorption was substantiated by examining the i.r. spectra of some of the derivatives of the amine (321). When the mono-methylated derivatives (324) were prepared (see later), two strong absorption bands were located at 1624 and 1630 cm^{-1} in the solid spectra of compounds (324a) and (324b) respectively. In these structures no tautomerism is possible and accordingly a $C{=}N$ absorption should not be present; only $C{=}O$ absorption is expected which must be the origin of these bands mentioned above.

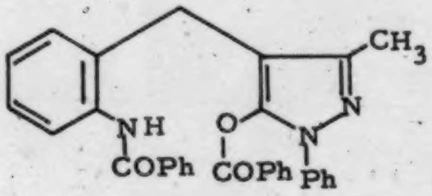


(324)

a, R = CH_3

b, R = Ph

On the other hand, the dibenzoyl derivative (325) and the triacetyl derivatives (326) will show $C{=}N$ absorption bands. These bands were found at 1600 cm^{-1} in the dibenzoyl derivatives (325) and at 1600 and 1595 cm^{-1} in the triacetyl derivatives (326a) and (326b) respectively, and apart from the acyl $C{=}O$ absorptions, no other bands were present in the 1600-1800 cm^{-1} region.



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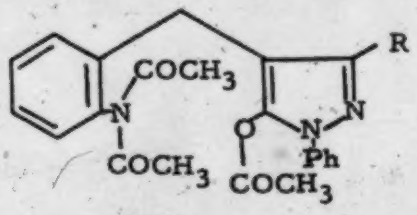


(326)

a, R = CH_3

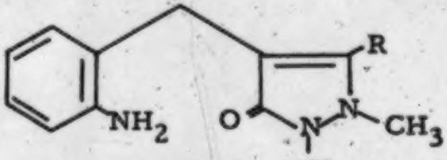
b, R = Ph

This, added to the above discussion, provides conclusive evidence that the strong absorption bands present around 1625 cm^{-1}

in the i.r. spectra of the solid amines (321) are actually due to a strongly bonded lactam C=O absorption. Accordingly, these amines are best represented by both the NH and OH forms, rather than by the CH form.

Some derivatives of 4-(2-aminobenzyl)-2-pyrazolin-5-ones (321a,b):

Methyl derivatives (324) of the amines (321a, 321b) were prepared by reacting them with dimethylsulfate. N-Methyl derivatives (324) were the only products obtained although theoretically, two other isomers (327 and 328) were possible. Evidence in support of the N-methyl structure was the presence of a three-proton signal at δ2.98 in the n.m.r. spectrum of the methylation product from (321a) and a similar signal at δ2.91 in the product from (321b). This chemical shift is similar to that of the N-methyl signal of antipyrine (329) and aminopyrine (330) which come to resonance at δ2.95 and 2.90 respectively. Methylation at C-4 was ruled out by the absence of a C=O absorption band near 1720 cm^{-1} (Katritzky and Maine, 1964)



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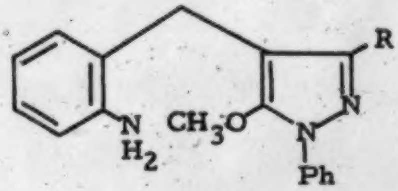

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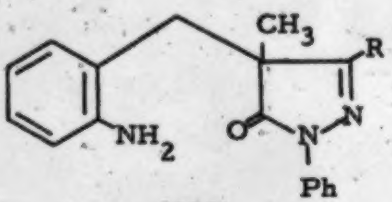
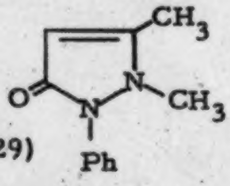


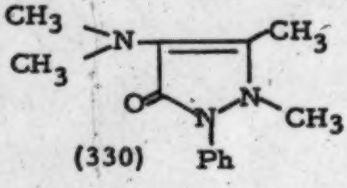
(328)

a, R= CH_3

b, R= Ph



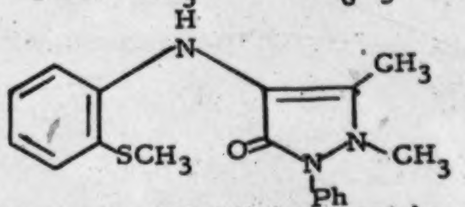
(329)



(330)

in the spectra of both methylated derivatives. These results are in agreement with the fact that it is easier to methylate at the N-2 rather than at the C-4 position of the pyrazolone ring (Wiley and Wiley, 1964). Methylation of 3-methyl-1-phenyl-2-pyrazolin-5-one(317 a) is known (Bodendorf and Raaf, 1955) to occur at N-2 when dimethyl sulfate is used as an alkylating agent. When the pyrazolone (317a) was treated with dimethyl sulfate under the same conditions used to prepare (324), only N-methylation occurred and antipyrene (329) was the single product isolated.

Additional evidence to confirm the presence of the N-methyl function in the methylation products was obtained from an examination of the mass spectra of both compounds. Molecular ions of m/e 293 and m/e 355 were present in the spectra of (324a) and (324b) respectively. The methyl derivative (324 a) displayed a strong fragment ion (97% of the base peak) at m/e 56 which corresponds to $CH_3-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow CH_3-\overset{+}{C}=N-CH_3$. This fragment was also the base peak in aminopyrine (330) and in the pyrazolone (408) which is described later in this study. Similarly, the strongest ion in the mass spectrum of the phenyl analog (324b) was at m/e 118 which corresponds to $C_6H_5-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow C_6H_5-\overset{+}{C}=N-CH_3$.



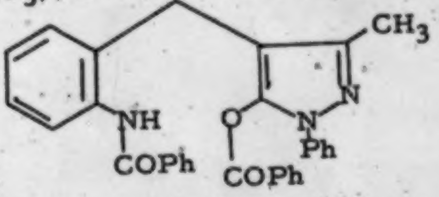
(408)

A relatively strong (M-30) fragment ion was observed in the spectra of both (324a) and (324b). An accurate mass measurement of this ion (m/e 325) in compound (324b) identified it as $C_{22}H_{17}N_2O$ and showed that it was formed by the expulsion of CH_4N

from the molecular ion. A metastable of m/e 297.55 suggested a direct fragmentation, $C_{23}H_{17}N_3O$-$CH_4N \longrightarrow C_{22}H_{17}N_2O$ and supported the previous conclusion that an N-methyl group was present in (324b).

- - -

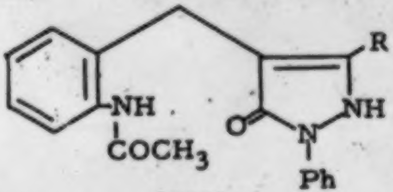
The action of benzoyl chloride on the amine (321 a) produced a dibenzoyl derivative identified as (325) from its elemental analysis ($C_{31}H_{25}N_3O_3$), i.r., n.m.r., and mass spectra. The i.r. spectrum (solid) (325) displayed two C=O absorption bands at 1645 cm^{-1} (NHCOPh) and at 1760 cm^{-1} (OCOPh) and an NH absorption band at 3315 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) showed a methyl signal at δ2.12, a methylene signal at δ3.8, an aromatic multiplet between δ6.8 and 7.9 (19 protons) and a D-exchangeable proton at δ8.0 (NH).



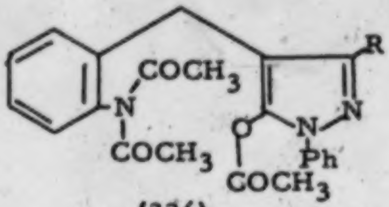
(325)

This compound was insoluble in sodium hydroxide which indicated that the labile proton in the pyrazolone ring was replaced during benzoylation. A carbonyl stretching frequency of 1760 cm^{-1} supports the proposed ester structure (325). Also, in the mass spectrum of (325), the molecular ion was at m/e 487, and fragmented initially by the expulsion of benzoyl (PhĊO) and benzoyloxy (PhCOȮ) radicals and a benzoic acid molecule. The presence of two strong metastables at m/e 275.06 and 273.65 respectively suggested that the last two expulsions were direct fragmentations of the molecular ion.

Acetylation of the amine derivatives (321a and 321b) by heating with acetic anhydride for one hour gave monoacetyl derivatives. However, when heating was prolonged, triacetyl products were isolated. These were identified as 4-(2-acetylaminobenzyl)-1-phenyl-2-pyrazolin-5-ones (332) and 5-acetyloxy-4-(2-diacetylaminobenzyl)-1-phenylpyrazoles (326) respectively.



(332)



(326)

a, R = CH_3

b, R = Ph

Due to their ability to enolize, the monoacetylated derivatives (332) were soluble in dilute alkali solutions. They analyzed correctly for $C_{19}H_{19}N_3O_2$ (332a) and $C_{24}H_{21}N_3O_2$ (332b) and the i.r. spectrum of each displayed two C=O absorption bands attributable to the amide and lactam functions. The mass spectrum (Fig. 2) of (332a) had a molecular ion at m/e 321 which fragmented initially by the expulsion of a water molecule, a ketene molecule and a $CH_3CO\dot{N}H$ radical to give ions a, b and c respectively. The fragmentation pathways and some of the fragment ions formed in the spectrum of this compound are tentatively identified in Scheme 3.

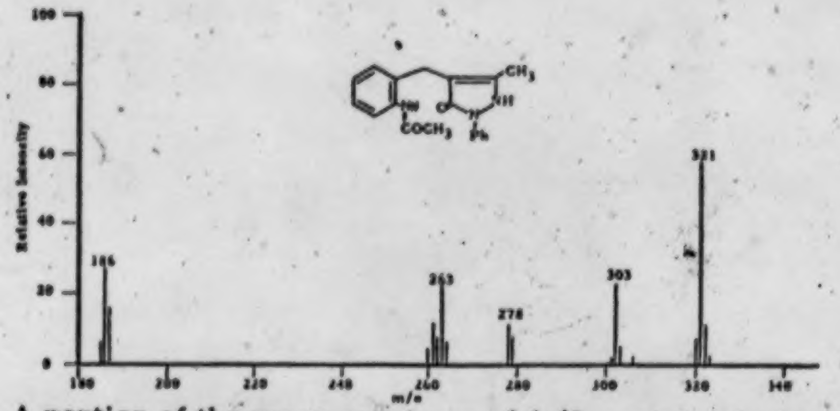
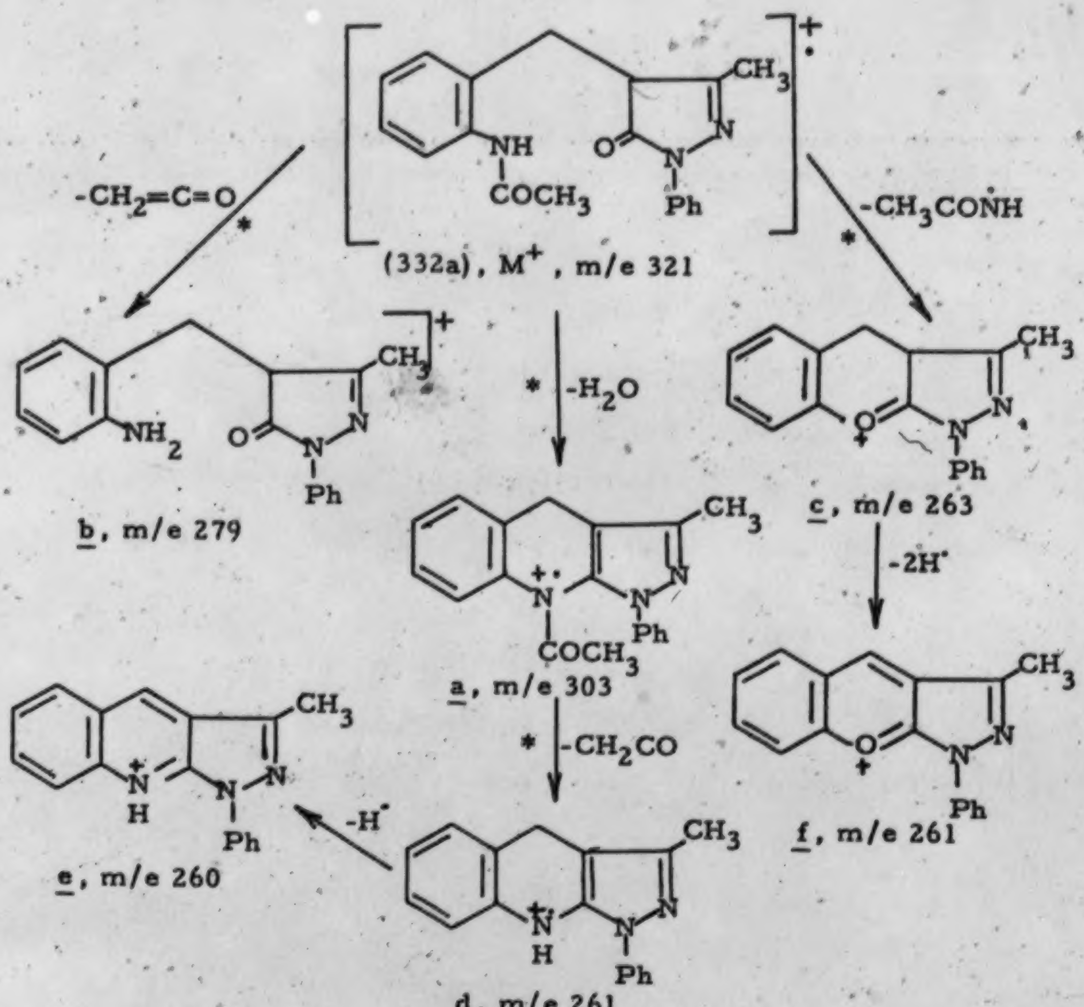


Fig. 2: A portion of the mass spectrum of 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).


CH3
NH
O
N
N
COCH3
Ph
-CH2=C=O
*
-CH3CONH
*
(332a), M+, m/e 321
NH2
b, m/e 279
* -H2O
c, m/e 263
-2H·
a, m/e 303
* -CH2CO
f, m/e 261
e, m/e 260
-H·
d, m/e 261

Scheme 3

Both triacetyl derivatives (326) dissolve slowly in dilute alkalis. When the alkaline solutions were acidified, they yielded the monoacetyl derivatives (332). The elemental analyses as well as the i.r., n.m.r., and mass spectra supported the proposed structures (326a and 326b). Both n.m.r. spectra displayed a six-proton signal for the N-diacetyl function, a three-proton signal for the O-acetyl group, a methylene signal and an aromatic multiplet. The i.r. spectra was devoid of any NH or OH absorption bands. The methyl derivative (326a) displayed three strong C=O bands at 1790 cm^{-1} ($OCOCH_3$), and at 1685 and 1730 cm^{-1} due to the N,N-diacetyl doublet (Grove _et al_, 1956). In the i.r. spectrum of the phenyl analog (326 b), the corresponding bands appeared at 1793, 1705 and 1718 cm^{-1}. The presence of the carbonyl absorptions of the N,N-diacetyl function at a higher frequency than the carbonyl absorption bands of the monoacetyl compounds (332) has already been commented upon (Abramovitch, 1957). However, the ester carbonyl absorption near 1790 cm^{-1} is unexpected and should be contrasted with the values of 1770 cm^{-1} for phenyl acetate (Witkop and Patrick, 1952; Grove _et al_, 1956). The reason may be the presence of bulky substituents in the _o_-position (c.f. Schubert and Saveeney, 1955).

The triacetylated derivative (326a) fragmented mainly by successive expulsions of two ketene molecules to yield the molecular ion of the mono-acetylated compound (332a). The $(M-42)^+$ ion (_a_) also expelled a water molecule to give a relatively strong ion of m/e 345 (Fig. 3, Scheme 4).

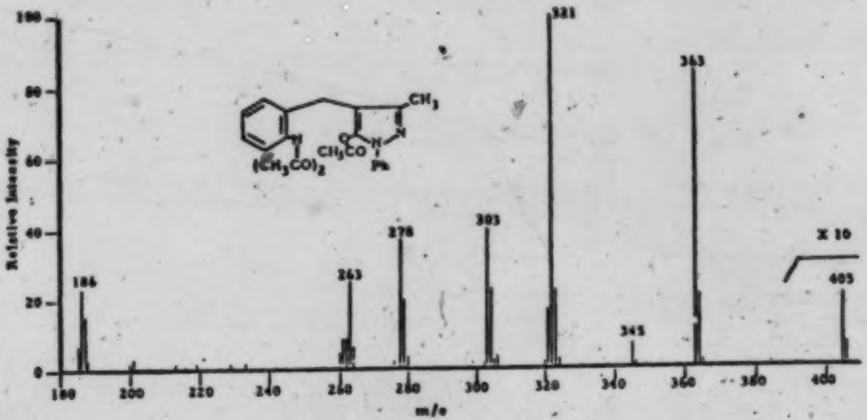
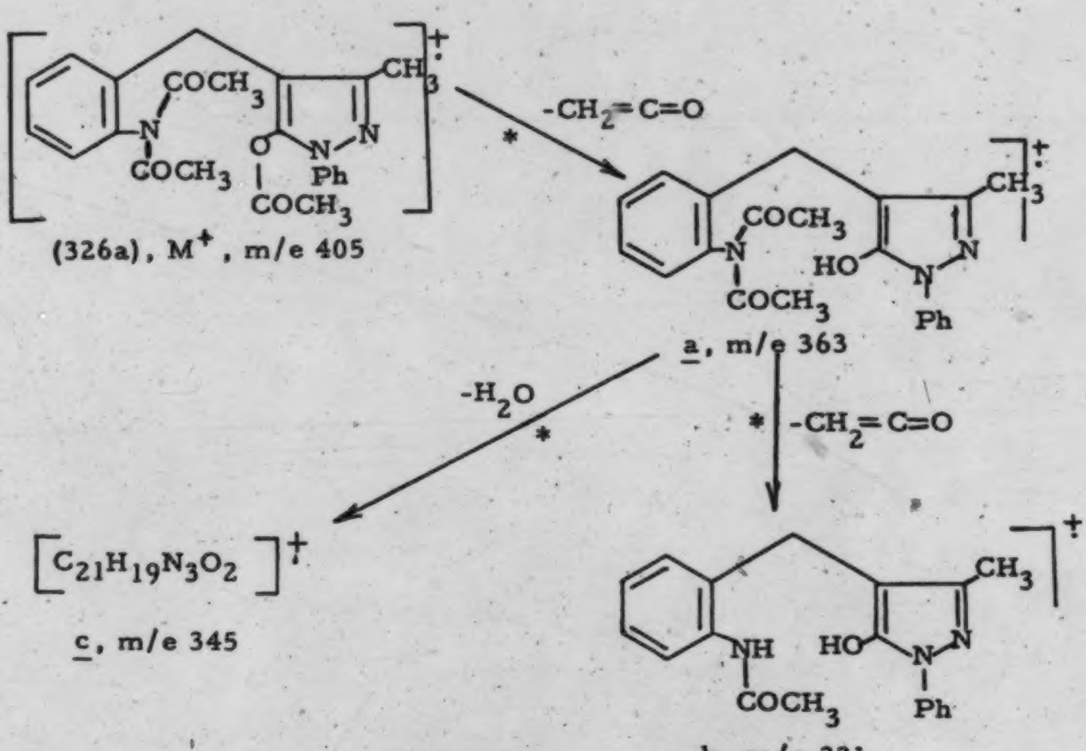


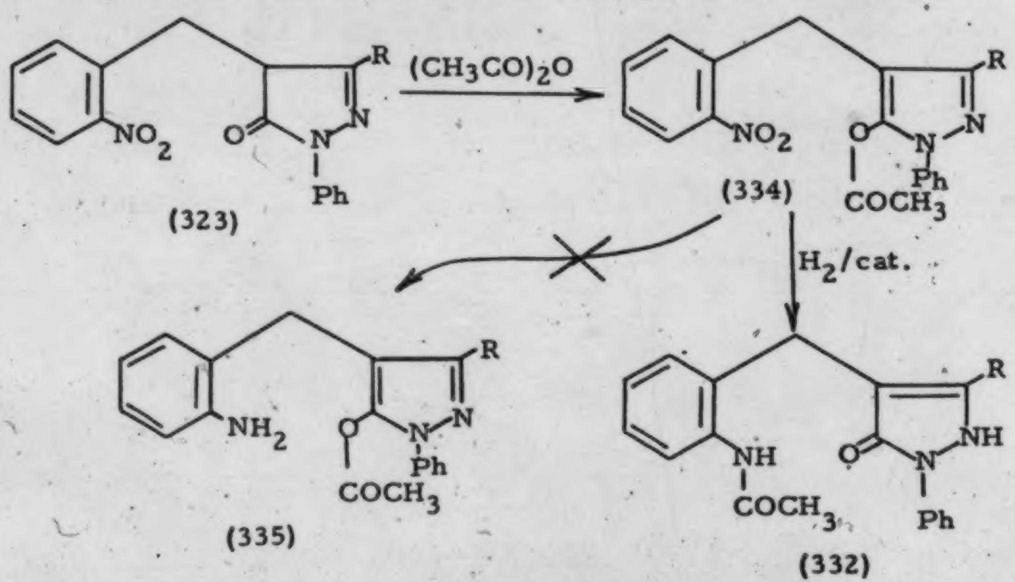
Fig. 3: A portion of the mass spectrum of 5-acetyloxy-4-(2-diacetylaminobenzyl)-3-methyl-1-phenylpyrazole (326a).


(326a), M^{+}, m/e 405
$-CH_2=C=O$
*
a, m/e 363
$-H_2O$
*
$-CH_2=C=O$
$[C_{21}H_{19}N_3O_2]^{+\cdot}$
c, m/e 345
b, m/e 321

Scheme 4

Attempts were made to prepare the O-acetyl derivatives (335) through the reduction of the 5-acetyloxy-4-(2-nitrobenzyl)-1-phenylpyrazoles (334). The latter compounds were prepared by treating the nitropyrazolones (333) with acetic anhydride. The presence of

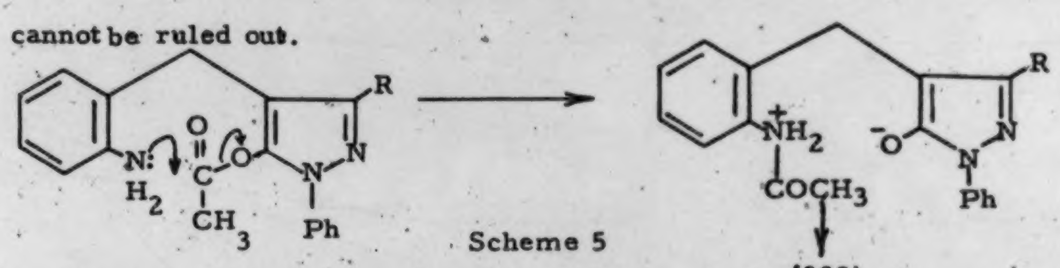
O-acetyl functions in the products was confirmed by i.r. spectroscopy (1781 cm^{-1} in 334a and 1790 cm^{-1} in 334b), by n.m.r. (O-COCH$_3$ protons came to resonance at δ 2.03 in 334a and δ 2.02 in 334b) and by mass spectral fragmentation (direct loss of CH$_3$COO$^\bullet$ radical from the molecular ion). When the O-acetyl compounds (334) were reduced either by catalytic hydrogenation over platinum or by sodium borohydride/palladium-charcoal in dioxane, oily products were obtained.



a, R = CH$_3$

b, R = Ph

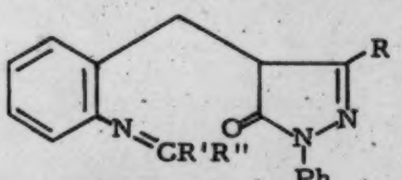
The only crystallizable compounds isolated were the N-acetyl derivatives (332) rather than the desired O-acetyl derivatives (335). Identification of these compounds was done by comparison with authentic samples prepared and described earlier. The isolation of such products indicated that the acetyl group, originally attached to the oxygen atom of the pyrazole ring, migrated to the amine function once the latter was formed. Such migration of acyl residues from oxygen to nitrogen (O → N) or vice versa (N → O) is a common phenomenon which occurs, for example, with all α-amino-β-hydroxy compounds in the aromatic, hydroaromatic and aliphatic series (Witkop and Patrick, 1952). Examples of 1,3-acyl migrations have also been demonstrated (Miller, 1965) and examples of acyl migrations involving different pairs of heteroatoms are known and have recently been reviewed by Akabori (1965) and by Pavlova and Rachiniskii (1968). Also, Tani et al (1964), reported some acyl exchange reactions between N-acyl lactams and amines, but no examples comparable to the one shown in this present study between the O-acetyl lactam and the amine function seem to have been reported. In this instance, the amine and acetyl group seem suitably orientated to allow this migration to occur intramolecularly (Scheme 5) although an intermolecular migration cannot be ruled out.



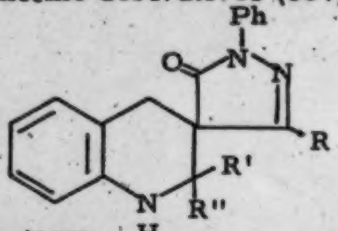
Scheme 5

(332)

The final piece of evidence sought in order to confirm the amine structure (321) was to attempt a preparation of Schiff bases (336) through the condensation of these amines with some aldehydes and ketones. However, Schiff bases were not isolated. Instead, the products cyclized to spiro-tetrahydroquinoline derivatives (337),



(336)



(337)

the formation and identity of which will be discussed in detail in a later section.

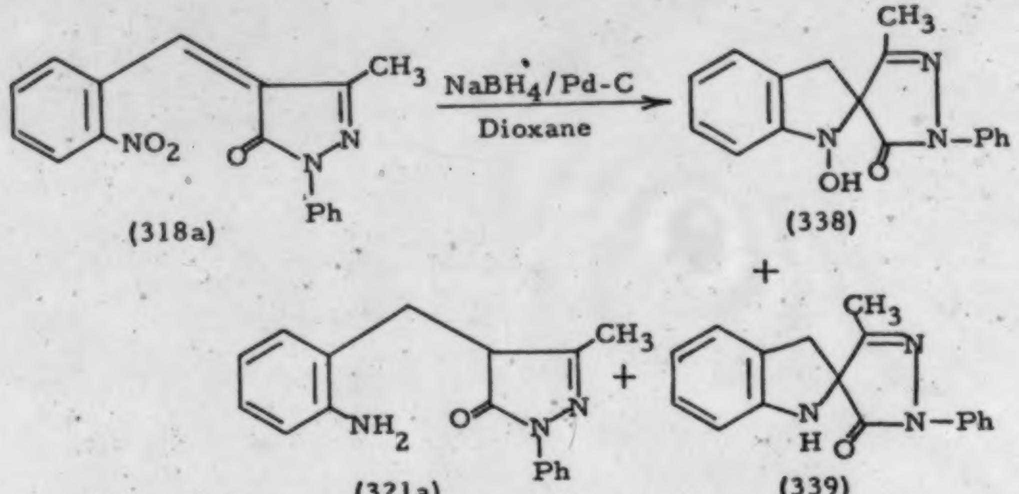
Method (C): Reductions in dioxane.

It is well known that metal hydride reductions are often influenced by the nature of the solvent used (Brown, 1962; Coutts, 1969). This fact led to a repeat of the sodium borohydride/palladium-charcoal reductions just described, in another solvent to determine whether this might facilitate cyclization to the desired N-hydroxy compounds. Coutts and his co-workers (Coutts and Wibberley, 1963; Coutts and Hindmarch, 1966) found dioxane to be a suitable solvent for their catalytic sodium borohydride reductions. This solvent was also used for the reduction of some 4-(2-nitrobenzylidine)-2-pyrazolin-5-ones (98) but the reduction products were left unidentified (Coutts and Edwards, 1966).

i) Reduction of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a).

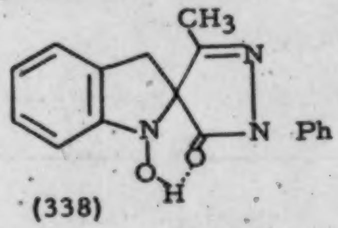
This reduction was repeated with some modification to the literature method (Coutts and Edwards, 1966). When hydrochloric acid was used to decompose the surplus hydride and precipitate the acidic products, a yellow impure solid was obtained. Replacing hydrochloric acid with acetic acid produced a white solid which was easily purified by fractional crystallization to yield three compounds. The major product was identified as the cyclic N-hydroxy compound, spiro-[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5-one)] (338). The other two products were spiro[(indoline-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (339) and the previously described amphoteric amine (321a).

The identity of the N-hydroxy compound (338) was based initially on the observations that it reduced Tollen's reagent and that it analyzed correctly for $C_{17}H_{15}N_3O_2$, a formula verified by the

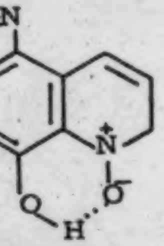


(318a) (338) (321a) (339)

presence of a molecular ion at m/e 293 in its mass spectrum. In the presence of alkali, this compound gave a purple-red color with triphenyltetrazolium chloride, a reaction which is claimed to be specific for hydroxylamine derivatives (Snow, 1954; Rogers, 1955). That the pyrazolone ring still remained intact was clear from the i.r. spectrum which showed a C=O absorption band at 1690 cm^{-1}. This C=O is present at a lower frequency than that usually demonstrated in 5,5-disubstituted pyrazolone derivatives. However, an intramolecular hydrogen bonding with the N–OH groups is possible in such a structure (338) in which the donor and the acceptor groups are in peri position. Katritzky and Logowski (1971c) described a similar effect in 8-hydroxyquinoline-1-oxide and its azo derivative (340). Support for hydrogen-



(338)



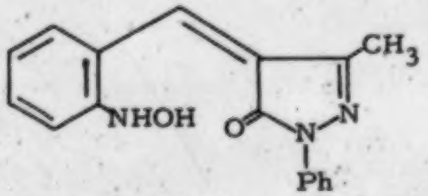
(340)

bonding in (338) is the position of the i.r. O–H stretching band which was broad and of low frequency centered at 3275 cm^{-1}.

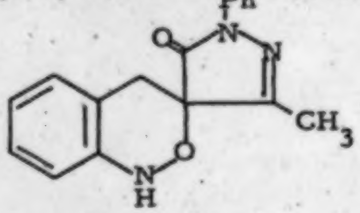
Another argument in favor of the cyclic structure (338) was the lack of solubility of this compound in dilute alkalis, a property shown by all pyrazolones having a hydrogen atom at C-4. This cyclization was not unexpected since the hydrogen atom at C-4 is known to be very reactive; it undergoes the characteristic condensation and substitution reactions of an active methylene group (Wiley and Wiley, 1964). Once the C-4 position is disubstituted, the acidity of the pyrazolone ring becomes so weak that it is now essentially neutral (Wiley and Wiley, 1964).

The n.m.r. spectrum of this compound (in DMSO-d_6) displayed a methyl signal at δ3.28, a slightly broad methylene signal at δ3.28, and a one-proton signal at δ9.67 which exchanged with deuterium. Assignment of this D-exchangeable signal to the N—OH function is consistent with some earlier reports (Kato and Yamanaka, 1965; Acheson et al, 1970; Schweizer and Kopay, 1972). The appearance of the two methylene protons as a broad singlet was not expected since these two protons are non-equivalent. However, this appears to be only a solvent effect since the n.m.r. spectrum repeated in pyridine displayed, for these methylene protons, a doublet of doublets with a geminal coupling constant of 16 Hz. Also, in pyridine, the N—OH signal appeared further downfield as a broad peak centered at δ12.1.

Initially, two other isomeric structures (315 and 341) were considered along with the N-hydroxy structure (338) for the major reduction product of (318a). The hydroxylamine structure (315) suggested by Pound (1970), was only a remote possibility since the benzylidine double bond would be reduced under the reduction conditions used. The sodium borohydride reduction of this double bond with dioxane as a solvent was demonstrated earlier. The presence of only one D-exchangeable proton and a methylene signal in the n.m.r. spectrum of this product completely ruled out the hydroxylamine formula (315). The isomeric structure (341) was a more serious possibility due to the fact that it is compatible with some of the i.r. and n.m.r. spectral data. However, the fact that the product isolated was neutral suggested that such a structure is not appropriate. Compound (341) is expected to be basic because it is known that the related isoxazolidines (cyclic 5-membered-NH-O-compounds) are strong bases (Quilico, 1962).



(315)



(341)

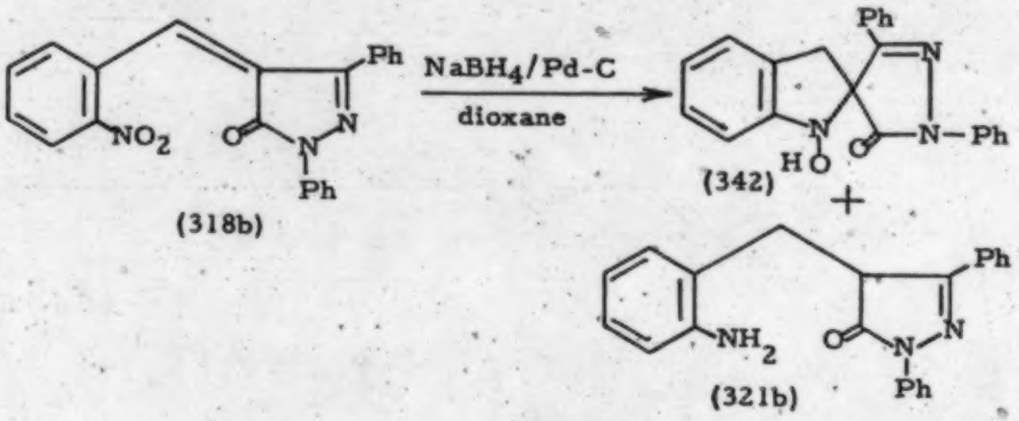
The mass spectral fragmentatation pattern of the product $C_{17}H_{15}N_3O_2$ was very helpful in confirming the appropriateness of the cyclic N-hydroxy structure (338). As will be discussed in detail later, the expulsion of an oxygen atom and a water molecule as well as the direct loss of an $\dot{O}H$ radical from the molecular ion were of special diagnostic value. Also, the chemical reactivity of this compound (including reduction, oxidation, acylations, sulfonation and reactions with nucleophiles) proved beyond any doubt that the N-hydroxy structure (338) was correctly assigned.

- - -

The minor products of the reduction of the pyrazolone (318a) were identified as the amine (321a) and the indoline (339). The former was identified by comparing its spectral properties with those reported earlier. The indoline (339) was identified by its elemental analysis ($C_{17}H_{15}N_3O$), its mass spectrum (M^+ at m/e 277) and its i.r. and n.m.r. spectra. The NH absorption band at 3305 cm^{-1} and the lactam C=O band at 1725 cm^{-1} were both at a higher frequency than the corresponding bands of the hydrogen bonded N-hydroxy indoline (338). The n.m.r. spectrum ($CDCl_3$) displayed an NH signal at $\delta 5.57$ (exchangeable with D_2O), a methyl signal at $\delta 2.09$, an aromatic multiplet (9 protons) and a methylene signal in the form of a doublet of doublets centered at $\delta 3.33$. The mass spectral fragmentation of this spiro-pyrazolone (339) and some other related compounds will be discussed in detail in a later section.

ii) Reduction of 1,3-diphenyl-4-(2-nitrobenzylidine)-2-pyrazolin-5-one (318b).

Reduction of compound (318b) with sodium borohydride/palladium-charcoal in dioxane was carried out in a similar manner to that described for the methyl analog (318a). In this case, only two products were obtained. The major one was identified as spiro-[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (342) while the minor one was found to be the previously described amphoteric amine (321b). Identification of (342) was based on its



(318b)

(342)

(321b)

elemental analysis ($C_{22}H_{17}N_3O_2$) as well as its physical and chemical properties. It reduced Tollen's reagent and gave a positive reaction with triphenyltetrazolium chloride. Its i.r. (N—OH band at 3347 and C=O band at 1696), n.m.r.(exchangeable N-OH signal at δ9.8, methylene signal at δ3.47 and a 14 proton aromatic multiplet between δ6.7 and 8.3) and mass spectra (expulsion of O, $\dot{O}H$ and H_2O from the molecular ion) were very similar to those of the methyl analog (338).

Reactions of Cyclic N-Hydroxyindoline Derivatives (338 and 342).

The chemical properties of aromatic hydroxylamines and hydroxamic acids have been studied in some detail. Fewer studies on cyclic hydroxylamines have been reported. Since some stable N-hydroxy compounds were prepared in the present study, a brief investigation of their chemical reactivity was made. The reactions studied, which could be of biochemical significance, were as follows:-

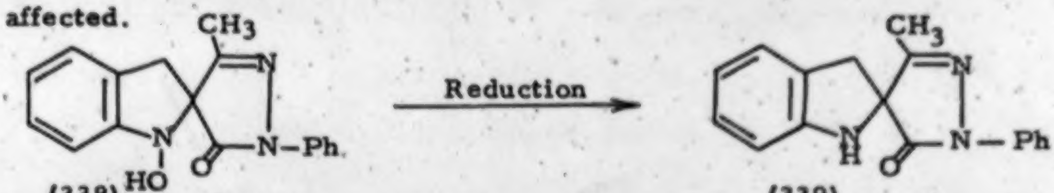
a) Reduction
b) Oxidation
c) Attempted dehydration
d) Reactions with nucleophiles
e) Acylation and sulfonation reactions
f) Methylation

a) Reduction:

The N-hydroxy function of cyclic hydroxylamines can be reduced to an NH function by various reducing agents including zinc and acids, phosphorous and hydroiodic acid, tin and hydrochloric acid, sodium hydrosulfite and lithium aluminum hydride. Catalytic hydrogenation over metals is also used for this purpose. However, in certain instances (Loudon and Wellings, 1960; Kato and Yamanaka,

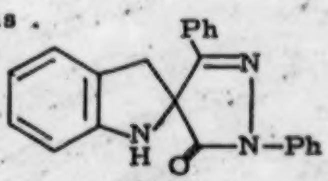
1965) such reductions do not occur.

In the present study, the N-hydroxy compound (338) was found to be smoothly reduced by catalytic hydrogenation over platinum, to give an almost quantitative yield of the cyclic amine (339). The same compound was also isolated when the reduction was carried out using iron and ferrous ammonium sulfate or zinc and ammonium chloride. Both reductions were performed in aqueous ethanol. In none of these reductions was the double bond in the pyrazolone ring affected.



(338) (339)

Similarly, reduction of the phenyl analog (342) using the same reducing agents yielded the amine, spiro[(indoline)-2,4'-(1',3'-diphenyl-1H-pyrazoline-5'-one)] (343). This compound analyzed correctly for $C_{22}H_{17}N_3O$ (M^+ = 339). Its i.r. spectrum displayed an NH absorption band at 3485 cm^{-1} while its n.m.r. spectrum ($DMSO-d_6$) showed a D-exchangeable one-proton signal at δ4.6, a two-proton methylene singlet at δ 3.5 and an aromatic multiplet which integrated for 14 protons.

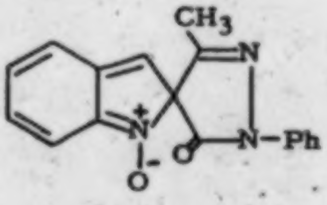


(343)

b) Oxidation:

Relatively mild oxidation will convert some cyclic N-hydroxy compounds to the corresponding nitrones. Frequently, this is done in the absence of any catalyst by simply bubbling air through solutions of the N-hydroxy compounds or by allowing solutions to stand in the atmosphere for several days at room temperature (Kato and Yamanaka, 1965). However, in most instances, a catalyst is required before oxidation takes place. Cupric acetate-ammonia, potassium ferricyanide and mercuric oxide have all been used successfully for this purpose.

Due to the susceptibility of the pyrazolone ring to oxidizing agents (Wiley and Wiley , 1964), an attempt to oxidize the N-hydroxyindoline (338) by bubbling air through its solution in tetrahydrofuran or aqueous ethanol was performed, but it failed to have any effect. Therefore, copper sulfate-ammonia, which was used extensively for this purpose by Brown et al (1959) was tried as a catalyst. Air was bubbled for several hours through a solution of (338) in aqueous ethanol, to which was added small amounts of copper sulfate and ammonia. Crystallization of the crude product gave a dark brown compound which, despite difficulty in getting a pure sample for elemental analysis, is believed to be the cyclic N-oxide (344). The mass spectrum of this compound displayed a molecular ion at m/e 291 which corresponds to the formulation $C_{17}H_{13}N_3O_2$. It liberated iodine from potassium iodide solution, a property common to N-oxides (Katritzky, 1956). Its i.r. spectrum was devoid of any amine or hydroxy absorption, and it displayed a carbonyl band at 1728 cm^{-1} which was located at a higher frequency than that of the

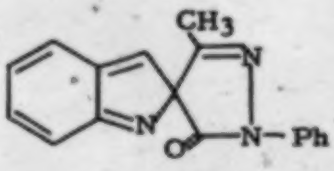


(344)

N-hydroxy compound (338) due to the lack of any hydrogen bonding. The n.m.r. spectrum ($CDCl_3$) had no D-exchangeable protons; it displayed only two signals, a methyl singlet at δ 2.07 and an aromatic multiplet between δ 6.7 and 8.2 (10 protons).

c) Attempted Dehydration:

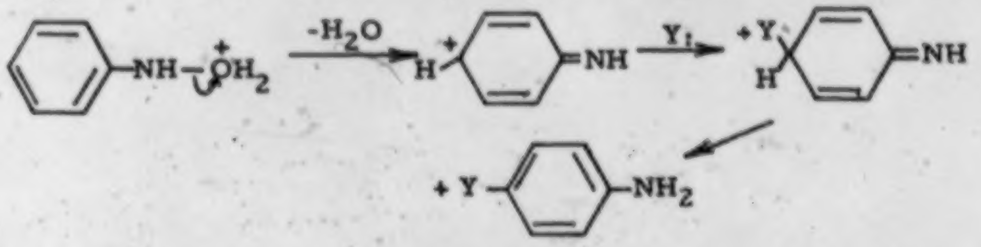
Due to the presence of a labile benzylic proton in the indoline ring, the dehydration of this N-hydroxy compound (338) was expected to proceed readily. Heating this compound with 10% sulfuric acid in methanol resulted in decomposition of the pyrazolone nucleus and the product isolated was not identified. When the same reaction was repeated at 0°, the pyrazolone ring was not affected. However, the desired product (345) was not formed; instead, a methoxylated compound, resulting from the nucleophilic attack of methanol on the benzene ring, was obtained. The same type of reaction happened when methanol was replaced with a mixture of dioxane and water; this led to a hydroxylated derivative. The formation and identification of both these products will be discussed in the next section.



(345)

d) Reactions with nucleophiles:

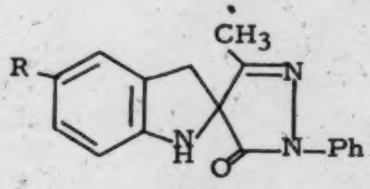
Phenylhydroxylamine rearranges in acid media to yield o- and p-aminophenol with varying amounts of azobenzene, azoxybenzene, aniline and nitrobenzene (Bamberger, 1921, 1925; Yukawa, 1950). When this reaction was carried out in the presence of nucleophilic species other than water, such as methanol, aniline or chloride ions, the corresponding ortho and para substituted anisidine, semidines and chloroanilines respectively were formed. Similar reactions were also observed by Kock (1887) and Robertson and Evans (1940). Heller et al (1951) formulated the mechanism of these nucleophilic reactions in an S_N1' manner, but they did not rule out the possibility of an S_N2' type reaction. Their proposed mechanism, for a para rearrangement, is illustrated in Scheme 6 in which Y could be any accessible and reactive nucleophilic molecule or anion.



Scheme 6

Various examples are now known of different nucleophilic reagents reacting with aromatic hydroxylamine and hydroxamic acid derivatives. Reactions in which the nucleophile is a halogen (Coutts and Pound, 1970; Stöhrer and Brown, 1970), oxygen (Gassman and Campbell, 1971), sulfur (Boyland et al, 1962; Edward and Whiting, 1971), nitrogen (Wölcke et al, 1969) or carbon (Takahaski and Kano, 1964) species have been reported. However, few of these reactions have been attempted with cyclic hydroxylamines.

In this study, different nucleophilic species, i.e. chloride ion, water, methanol and acetic acid, were reacted, in acidic media, with the N-hydroxy compound (338). In each case, it was deduced that a 5-substituted indoline derivative (346) was obtained. The preparation and structural elucidation of these compounds are now described.



(346)

a; R= Cl

b; R= OCH_3

c; R= OH

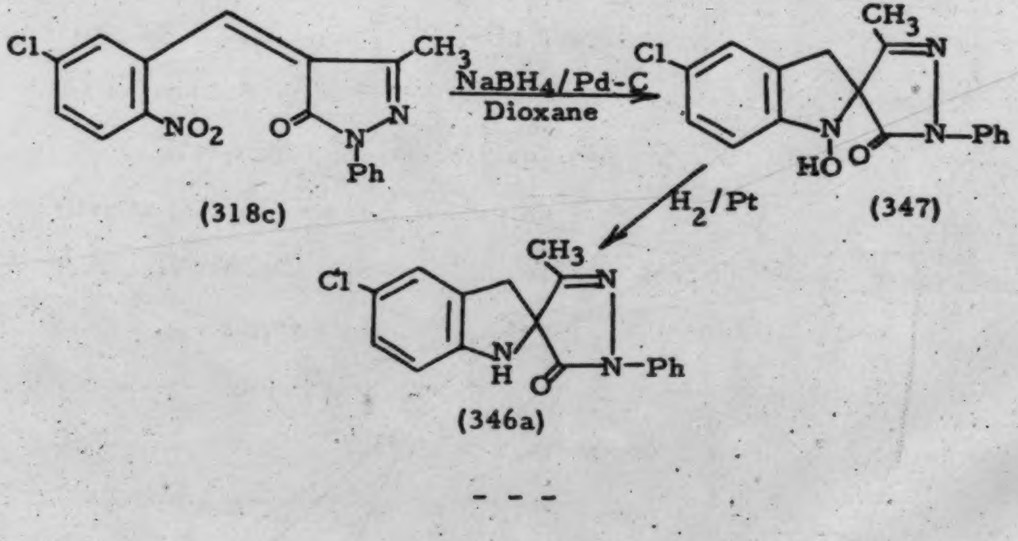
d; R= $OCOCH_3$

- - -

When hydrogen chloride was bubbled through a cold solution of the N-hydroxy compound (338) in tetrahydrofuran, a black semi-solid product was obtained. Chromatography of this product on a silica gel column, yielded spiro-[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346a) as a crystalline solid. This compound was identified by its elemental analysis ($C_{17}H_{14}ClN_3O$) as well as its spectral properties. The i.r. spectrum displayed C=O and NH absorptions. A methyl signal, a methylene doublet of doublets, an 8-proton aromatic multiplet and an N—H signal were present in the n.m.r. spectrum. The location of the chlorine atom in the product (346a) was suggested from the ample literature evidence that when hydrochloric acid and other nucleophilic reagents react with aromatic hydroxylamines, p-substituted amines are the major products isolated (Bamberger, 1925; Robertson and Evans, 1940; Coutts and Pound, 1970). However, confirmatory evidence could not be obtained from examining the n.m.r. spectrum of the product since the aromatic signal was complex and could not be easily interpreted.

This location of the chlorine atom became more significant when another isomeric chlorinated compound was obtained, as a by-product, by the action of acetyl chloride on the hydroxylamine (338) in benzene. Both these compounds analyzed correctly for $C_{17}H_{14}ClN_3O$ and displayed very similar mass spectra but their melting point, i.r. and n.m.r. spectra were different. Therefore, it was found necessary to prepare an authentic sample of (346a) for comparison purposes.

3-Chloro-6-nitrobenzaldehyde (316b) was condensed with 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) and the product (318c) was reduced with sodium borohydride and palladium-charcoal in dioxane. Spiro [(5-chloro-1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (347), $C_{17}H_{14}ClN_3O_2$, was isolated and identified from its physical and chemical properties which were similar to those of the other N-hydroxyindolines (338) and (342). Catalytic hydrogenation of (347) over platinum yielded the 5-chloroindoline (346a). Comparison of the spectral data and melting points of this compound with those of the product obtained by treating (338) with hydrogen chloride proved that both were identical.



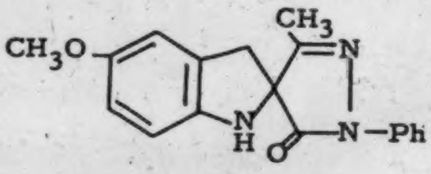
(318c)

(347)

(346a)

- - -

Heating the N-hydroxy compound (338) with methanol in the presence of a catalytic amount of sulfuric acid, resulted in decomposition. When this reaction was repeated and the reaction mixture left for 12 hours at 0°C, a dark green solution was obtained from which was isolated a colorless compound identified as spiro [(5-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346b). This structure was assigned for the following reasons: the product



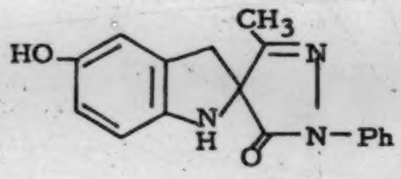
(346b)

analyzed correctly for $C_{18}H_{17}N_3O_2$ and its mass spectrum displayed a molecular ion at m/e 307, and showed, with minor differences, fragmentation patterns similar to those of the indoline (339) and the 5-chloroindoline (346a). These are described in more detail in a subsequent section. The i.r. spectrum had C=O and NH absorption bands at 1710 and 3310 cm^{-1} respectively. The n.m.r. ($CDCl_3$) displayed two methyl signals, a methylene doublet of doublets signal, a broad NH signal and an aromatic 8-proton multiplet. The complexity of the aromatic signal did not allow deduction of the exact location of the OCH_3 group but the pattern displayed for this signal was very similar to that in the spectrum of the 5-chloroindoline (346a). Accordingly, the methoxy substituent was assigned to the 5-position.

A better yield of this compound was obtained when methanolic sulfuric acid was replaced with a solution of boron trifluoride in methanol. This observation was the result of an attempt to methylate the N-hydroxy function by the use of diazomethane in methanol, with boron trifluoride as a catalyst. Acid catalyzed nucleophilic attack by methanol occurred rather than methylation of the N-hydroxy function, and the only product isolated was the 5-methoxy compound (346b).

- - -

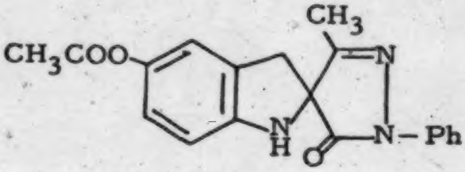
When the N-hydroxy compound (338) was reacted with a mixture of dioxane and water in the presence of catalytic amounts of sulfuric acid, an alkali-soluble product was isolated. Although no satisfactory analysis was obtained from this product, its i.r., n.m.r. and mass spectra (M^+ at m/e 293) suggested that it was the 5-hydroxyindoline (346c).



(346c)

- - -

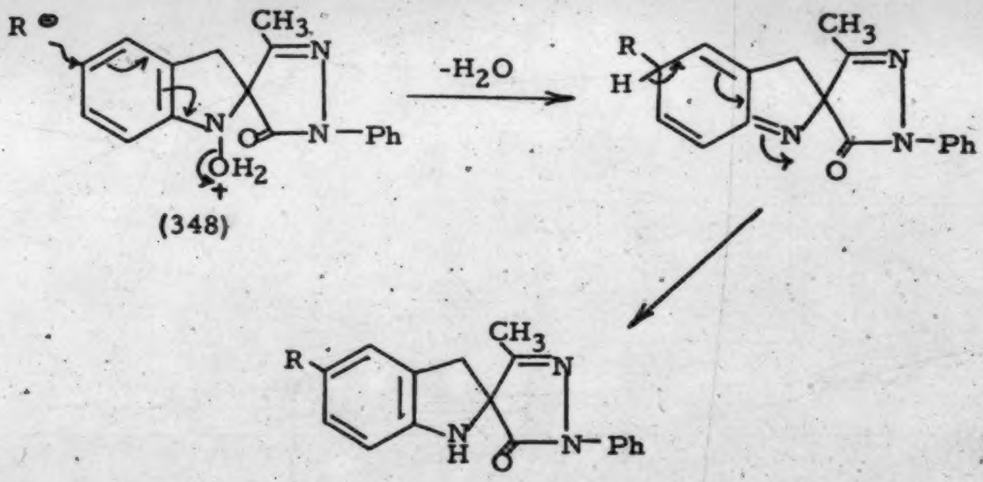
The related 5-acetoxy derivative (346d) was obtained by heating (338) with glacial acetic acid for one hour. This compound was identified by its elemental analysis ($C_{19}H_{17}N_3O_3$), mass spectrum (M^+ at m/e 335), i.r. spectrum (ester and lactam C=O and N—H absorption) and n.m.r. spectrum (two methyl signals, one D-exchangeable N—H proton, a methylene signal and an 8-proton aromatic multiplet.



(346d)

- - -

The formation of these 5-substituted indoline derivatives (346a-d) apparently involves a nucleophilic attack at the 5-carbon atom of the protonated N-hydroxy compound (348). However, it is not known whether this reaction is of the S_N2' (Scheme 7) or S_N1' (Scheme 8) type. An S_N2' mechanism was proposed recently by

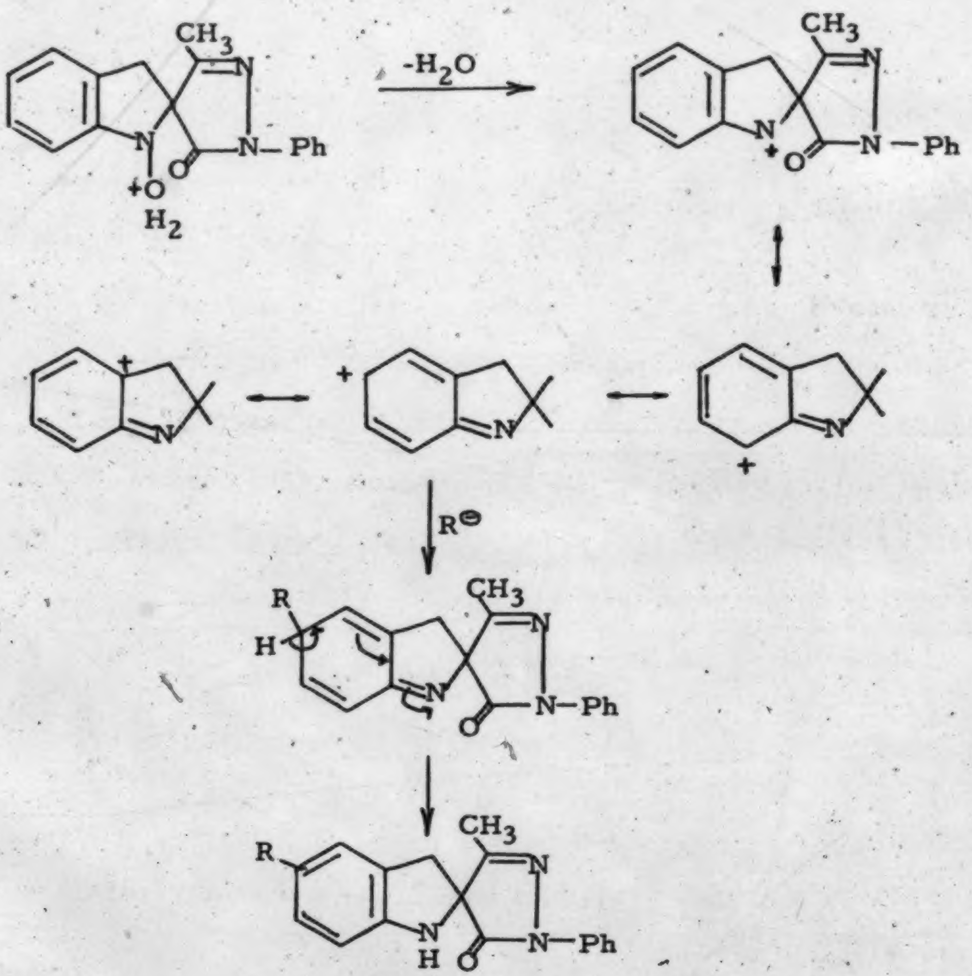


(348)

(346)

Scheme 7

Coutts and Pound (1970) for the attack of the chloride ion on some related hydroxylamines and hydroxamic acids. The alternative S_N1' type mechanism was proposed earlier by Heller et al (1951) and is supported by some recent studies by Gassman et al (1968, 1971, 1972).



(346a-d)

Scheme 8

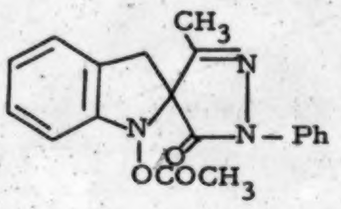
e) Acylation and sulfonation reactions:

Cyclic hydroxylamines react with acetyl, benzoyl and sulfonyl chlorides to form acetates, benzoates and sulfonates respectively. Acid anhydrides have also been used frequently as acylating agents. However, in many cases the acyloxy and sulfonyloxy derivatives cannot be isolated because they undergo molecular rearrangements. In order to determine the behavior of the cyclic N-hydroxy compounds prepared in this investigation towards some acylating and sulfonating agents, their reactions with acetic anhydride, acetyl chloride, p-chlorobenzoyl chloride and p-toluene sulfonyl chloride were studied. Besides the few N-acetoxy derivatives obtained, some rearrangement and halogenated products were also isolated and identified.

i. Reactions with acetic anhydride

Previous studies have shown that the cyclic N-acetoxy carbonyl function gives rise to an i.r. absorption band in the region of 1800 cm^{-1} and the presence of this absorption band is very diagnostic (Freeman, 1958; Loudon and Wellings, 1960). It was desirable, therefore, to acetylate the cyclic N-hydroxy compounds (338 and 342) as a means of confirming their structures and to study the chemical behavior of these N-acetyloxy products. A number of conventional acetylation procedures were attempted but most of them led to the formation of different rearrangement and decomposition products. The only successful method was to react the N-hydroxy compound in pyridine at -10°C with cold excess acetic anhydride for a 24 hour period. In a few instances, the N-acetyloxy derivatives crystallized from the reaction mixture, but in most cases ice-cold water had to be added to liberate the product. The acetyloxy products isolated were stable for several weeks at 0°C but decomposed rapidly on standing at room temperature. Earlier, when this acetylation process was performed at room temperature, no acetyloxy derivatives were obtained. The same happened when the reaction mixture, after being added to ice-cold water, was extracted with cold ether. Both procedures resulted in rearrangement and decomposition of the N-acetyloxy derivatives.

The acetylated product obtained from the N-hydroxy compound (338) was identified as spiro [(1-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5-one)] (349). This compound analyzed correctly for $C_{19}H_{17}N_3O_3$, a formula supported by the presence of a molecular ion at m/e 335 in its mass spectrum. That



(349)

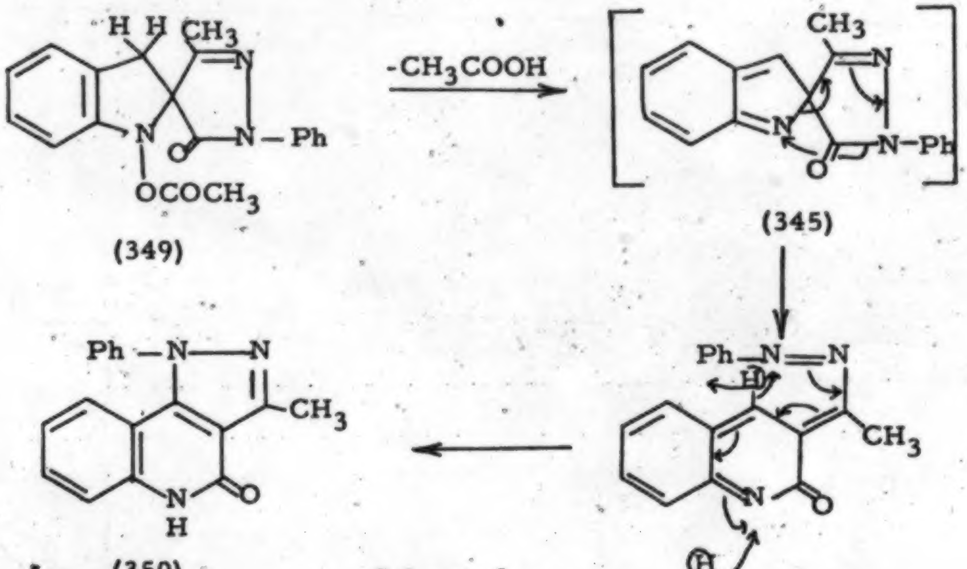
O-acetylation had occurred was confirmed by the presence of an N-acetyloxy C=O absorption band at 1790 cm^{-1}. In addition, a lactam C=O band was located at 1723 cm^{-1} and the spectrum was devoid of any O–H or N–H bands. The n.m.r. spectrum (in $CDCl_3$ or DMSO-d_6) showed two methyl signals at δ 2.14 ($C-CH_3$) and 2.05 ($OCOCH_3$), an aromatic multiplet (9 protons) and the methylene group signal as a doublet of doublets (J=16.5 Hz). This spectrum had to be measured directly after dissolving in cold solvent because, in both solvents used, the compound decomposed and/or rearranged very rapidly; the N-acetyloxy signal disappeared with the appearance of some new signals and the spectrum became very complicated.

Heating the N-acetyloxy compound (349) with methanol or ethanol yielded two different crystalline products. The first was identical to the 5-acetyloxy derivative (346a) obtained earlier by the nucleophilic attack of acetic acid at C-5 (see Scheme 7). The second product (designated compound A) remains unidentified, although it is known from its elemental analysis ($C_{17}H_{13}N_3O$) and its mass spectrum

(M^+ , m/e 275) that it is a result of the loss of acetic acid molecule from the parent N-acetoxy compound (349). The same compound was also isolated during attempts to methylate or sulfonate the N-hydroxy compound (338).

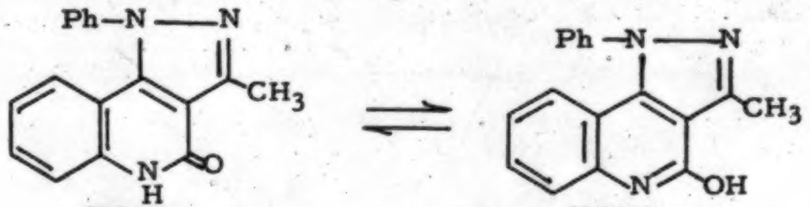
The possibility of product (A) being the dehydrated (345) was first considered but a study of the chemical and physical properties of (A) ruled out this possibility. The i.r. spectrum of A when crystallized from ethanol showed absorption bands at 3410 (NH?) and at 1625 and 1640 cm^{-1} (C=O?). A different spectrum was obtained when the same compound was crystallized from acetic acid giving (A') or when (A) was heated to about 200°C for a few minutes. The absorption bands at 3410 cm^{-1} and the doublet at 1625 and 1640 cm^{-1} were replaced with a broad band between 2500 and 3300 cm^{-1} and a strong absorption at 1640 cm^{-1}. This suggested that compound (A) may either have dimerized or be present in two different forms ($A \rightleftharpoons A'$). Both these forms were found to be interchangeable; either one can be obtained by crystallization from the appropriate solvent.

The n.m.r. of both forms had a three-proton signal at δ2.63, an aromatic multiplet between δ7.0 and 8.5 (~9 protons) and a one-proton broad signal between δ4.0 and 5.1 (exchangeable with D_2O). The presence of the methyl signal at a lower field (δ2.63) than usually demonstrated by the pyrazolone methyl group (around δ2.0) suggested that a rearrangement process might have occurred which destroyed the pyrazolone ring. Compound (350), the formation of which might be possible by the process outlined in Scheme 9 was considered and found to fit most of the chemical and physical properties demonstrated by the product ($A \rightleftharpoons A'$). This compound (350)



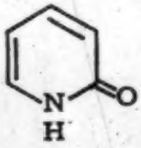
Scheme 9

might exist in two forms (350a $\rightleftharpoons$ 350b) which could explain to some extent the difference in the i.r. spectra of (A) and (A'). The

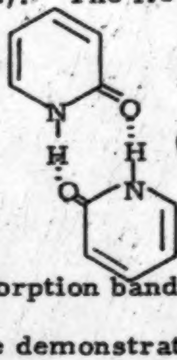


(350a) (350b)

possibility of dimerization of (A) must also be considered in view of the fact that the structurally related pyridin-2-ones e.g. (351) are known to exist as hydrogen-bonded dimers (352). The i.r. spectra



(351)



(352)

of these dimers displayed very broad N–H absorption bands in the region 2300-3200 cm^{-1}; free N–H bands were demonstrated in dilute chloroform solutions at around 3400 cm^{-1} (Katritzky and Amber, 1963).

The presence of carbonyl absorption at 1640 and 1625 cm^{-1} (doublet?) in (A) and at 1640 cm^{-1} in (A'') is also in agreement with structure (350) since quinolin-2-ones show carbonyl absorption between 1626 and 1660 cm^{-1} (Bellamy, 1968; Katritzky and Ambler, 1963).

A structure such as (350) could also explain the behavior of product (A) under electron impact (Fig. 4). In addition to the molecular ion, the main fragment observed was the (M-1) ion at m/e 274. A stable aromatic system (b) could be formed by the expulsion of a hydrogen atom from the molecular ion (Scheme 10).

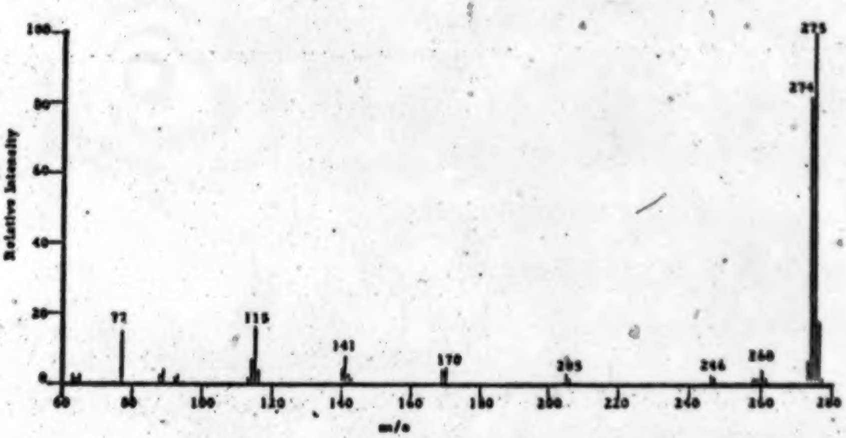
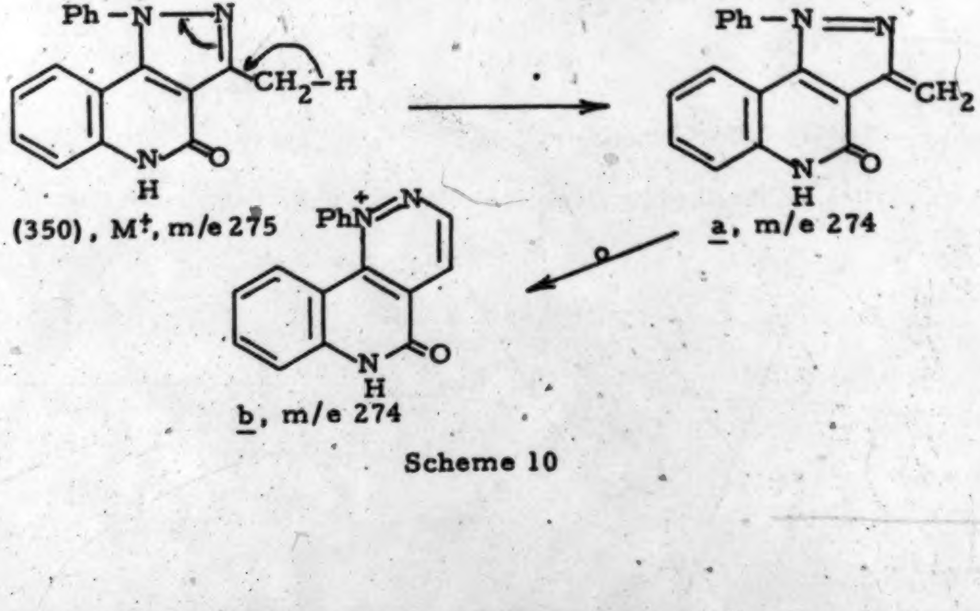
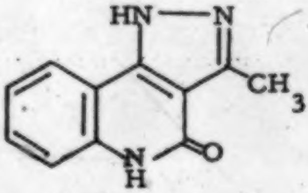


Fig. 4: A portion of the mass spectrum of compound (A), M^{+}=275.



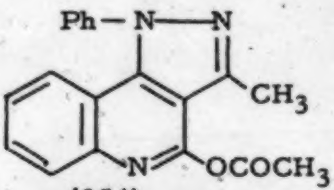
Scheme 10

In addition to these physical and chemical properties already discussed, the high melting point (306-7°) of both (A) and (A') is consistent with the proposed structure (350). A related compound, 4,5-dihydro-3-methyl-4-oxo-1H-pyrazolo[4,3-C]quinoline (353) was prepared by Coutts and Wibberley (1963) and was found to have a melting point higher than 350°C.

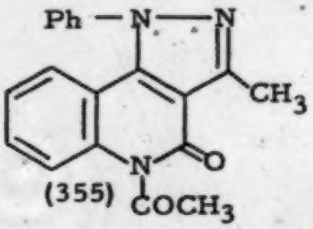


(353)

A chemical property that cast doubt on the assignment of (350) to product (A) was the ease with which this compound acetylated with acetic anhydride. This was not expected since 2(1H)-pyridones and related compounds acetylate only through their salts, such as the sodium (Curtin and Engelmann, 1968) or thalium (I) salts (McKillop and Zelsko, 1968). In addition, acetylation of (350), if it occurred, might be expected to yield the O-acetyl derivative (354) rather than

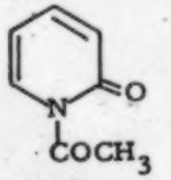


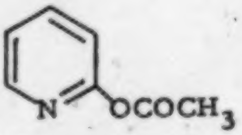
(354)



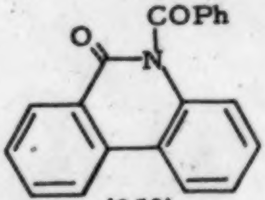
(355)

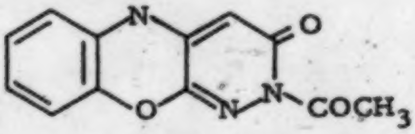
the N-acetyl compound (355). This was the case with 2(1H)pyridone (351) which yielded only the O-acetyl derivative (357) when its thallium (I) salt was acetylated. The N-acetyl derivative (356) was formed at -40°C but most of it rearranged at room temperature to (357) (McKillop and Zelesko, 1968). However, the possibility of O-acetylation of (350) was ruled out by the presence of two $C=O$ absorption bands at 1664 and 1730 cm^{-1} in the i.r. spectrum of the mono-acetylated product, $C_{18}H_{15}N_3O_2$ ($M^{\dot{+}}$ = m/e 317).


(356)

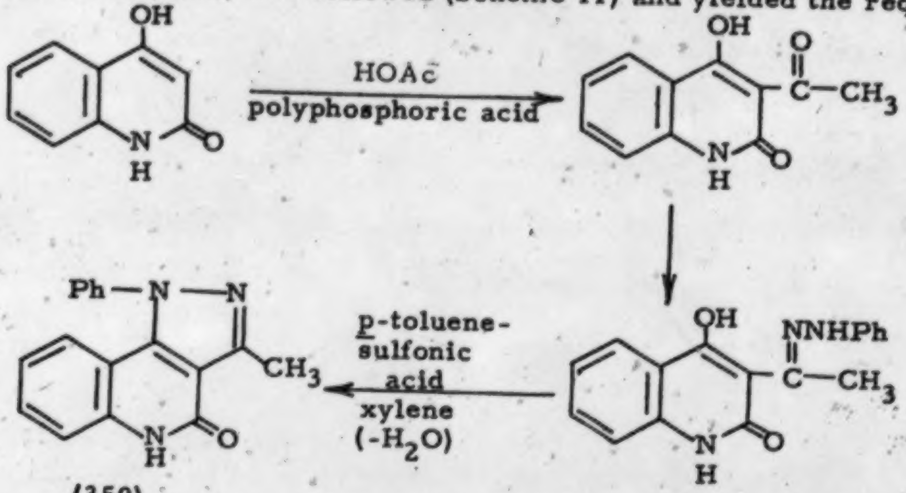

(357)

Reference by Curtain and Engelmann (1968) to the N-benzoyl derivative (358) was encouraging since it showed that this type of acyl derivative is accessible. Gortinskaya et al (1973) also prepared some related N-acetyl derivatives (359), the structures of which were confirmed with i.r. and u.v. spectral data. The two carbonyl bands in (358) were located at 1656 and at 1733 cm^{-1}; the latter is due to the N-benzoyl function. These values are comparable to those obtained from the acetyl derivative of (350), but this is not a very accurate comparison since a benzoyl compound is being compared with an acetyl derivative. However, the N-acetylated compound (359) had C=O absorption bands at 1680 and at 1730 cm^{-1}; the latter was shown to be due to the N-acetyl function. Both these values are similar to those shown by the acetyl derivative of (350), which suggested that its structure might indeed be (355).


(358)


(359)

A literature search for the pyrazolocarbostyryl derivative (350) revealed that it was a known compound prepared earlier by three independent investigators through different pathways (Knorr and Jodicke, 1885; Musierowicz et al, 1929; Vul'fson and Zhurin, 1962). In all cases, the reported melting points, although high (261°, 273° and 277°), were not the same as that of the dehydrated product (A) although in this range, the rate of heating might account for this difference. It is also possible that impure (350) was isolated in earlier studies. Accordingly, it was decided to prepare (350) to compare it directly with the dehydrated product (A). The method reported by Vul'fson and Zhurin (1962) was followed (Scheme 11) and yielded the required 3-methyl-5-phenyl-pyrazolo-(4,5-C)carbostyril (350).



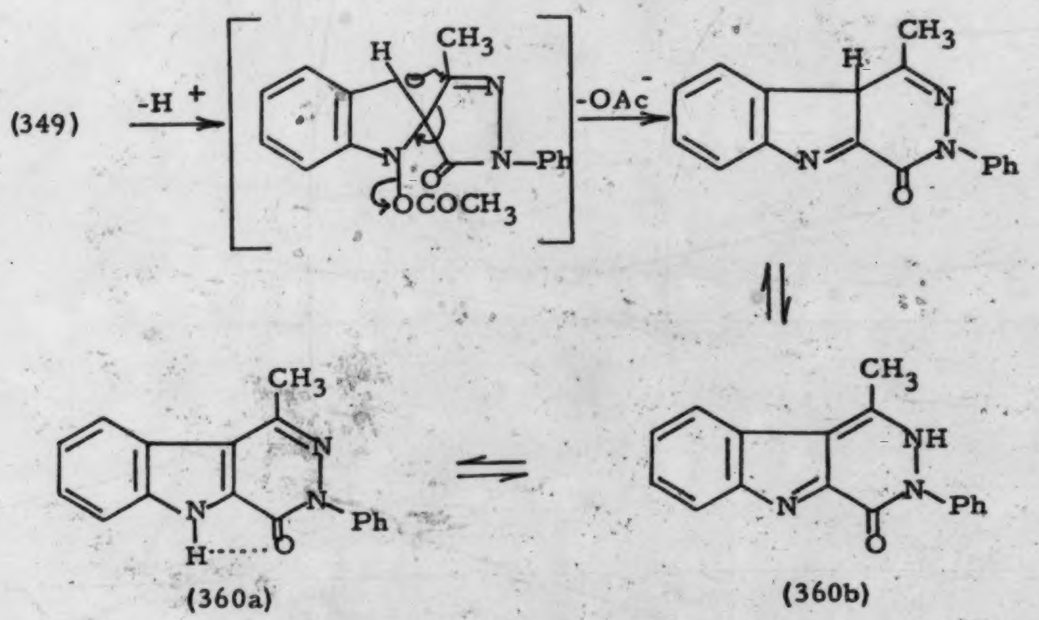
(350)

Scheme 11

A direct comparison between synthetic (350) and the deacetylated product (A) indicated non-identity. The i.r. spectrum of (350) (ν N–H between 2000 and 3220, ν C=O at 1666) and its n.m.r. spectrum (CH_3 at δ 2.61, NH or OH at δ 13.2 and nine aromatic protons between δ 6.9 and 7.8) were very similar to those of (A) but not identical. The pyrazolocarbostyryl (350) was also found to be neutral, but an attempt to acetylate it directly by heating with acetic anhydride for 12 hours failed to yield any acetylated product.

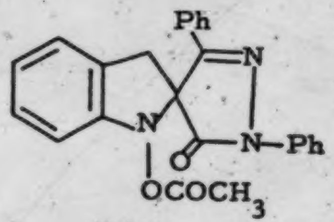
This non-identity of (350) with (A) demanded a reappraisal of the data accumulated for compound (A). It had a molecular formula $C_{17}H_{13}N_3O$, nine aromatic protons, three methyl protons, a labile proton (deuterium exchangeable) and a C=O group which absorbed i.r. irradiation at a frequency lower than the pyrazoline C=O group. In the n.m.r. spectrum the chemical shift of the methyl-protons signal was further dowfield than normally observed for the 3-methyl-5-pyrazolone methyl signal which suggested that compound (A) did not contain an intact pyrazoline ring such as that present in the spiropyrazolone (349).

It is now realized that the acetylated product (349) might rearrange in the manner shown in Scheme 12, thus providing another possible compound, the pyridazinoindole (360) to explain all the data accumulated for compound ($A \rightleftharpoons A'$). Lack of time, however, prevented studies to confirm this hypothesis.



Scheme 12

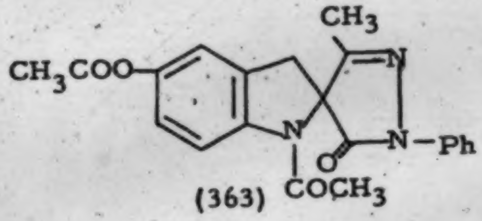
Acetylation of the cyclic N-hydroxyindoline (342) with acetic anhydride and pyridine at -10°C yielded an N-acetoxy derivative identified as spiro[(1-acetyloxyindoline)-2,4'-(1,3'-diphenyl-1H-pyrazolin-5-one)] (361) by its elemental analysis ($C_{24}H_{19}N_3O_3$) and by similarities of its spectral data with those of the methyl analog



(361)

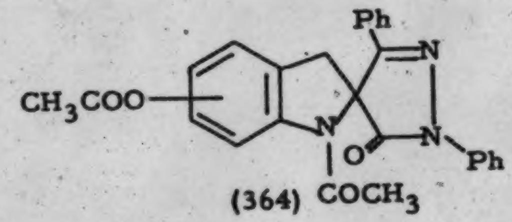
(349). It was noted that the acetyloxy derivative (361) was relatively stable at room temperature and in cold solvents. Rearrangement still occurred in solution but at a much lower rate than that demonstrated by the methyl analog (349). Heating (361) in ethanol produced only one rearrangement product of formula $C_{24}H_{19}N_3O_3$. Infrared evidence supported the presence of an NH and two C=O groups (lactam and ester) in the molecule. The n.m.r. spectrum had signals which could be ascribed to $COCH_3$, CH_2, NH and thirteen aromatic protons. Based on these data this compound was identified as spiro[(x-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (362). Although it is most likely that (362) is substituted at the 5-position as was the case with the methyl analog (346d), the exact position of the substituent was not determined due to the complex nature of the aromatic signal in the n.m.r. spectrum and due to the lack of an authentic sample.

When the N-hydroxy compounds (338 and 342) were heated with acetic anhydride or with a mixture of acetic anhydride and acetic acid, no N-acetyloxy derivatives were isolated. In the case of (338), two products were obtained, the major product being the dehydrated compound (A) discussed earlier while the minor product was shown to be a diacetylated compound, $C_{21}H_{19}N_3O_4$ which was assigned structure (363). The i.r. spectrum showed three C=O bands at 1667 (cyclic amide), 1715 (lactam) and 1760 cm^{-1} (ester) and was devoid of any NH or OH absorption. The n.m.r. spectrum displayed three methyl signals at δ2.02, 2.3 and 2.50 and a complex aromatic multiplet which did not assist in the assignment of the position of the acetate group on the ring. This, however, was deduced to be at C-5 in agreement with the mode of formation, and by comparison with similar products described earlier such as (346d).



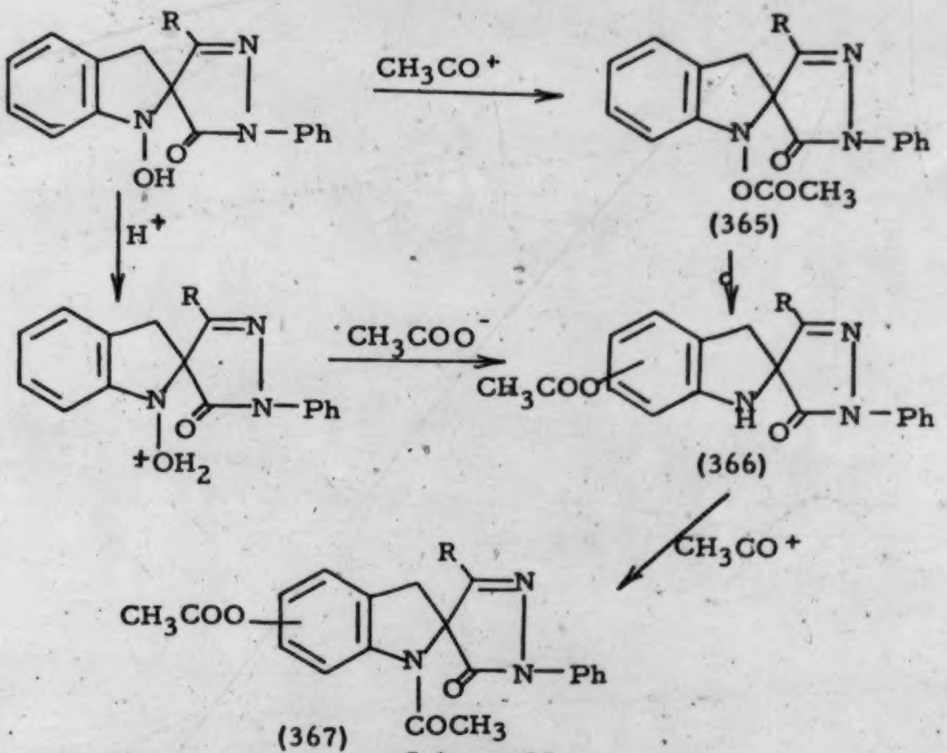
(363)

Heating the N-hydroxy compound (342) with acetic anhydride yielded a diacetate derivative which could not be obtained pure. Its mass spectrum displayed a molecular ion at m/e 439 which fragmented in the same way as the diacetate (363) and its i.r. and n.m.r. spectra resembled those of compound (363). This led to its identification as (364). The position of the acetate group on the ring was not determined.



(364)

The diacetates (363) and (364) could be formed in two ways as shown in Scheme 13. The first is the formation of the N-acetyloxy derivative (365) followed by migration of this acetyloxy group to the ring carbon. The second is the direct nucleophilic attack by the acetate anion. The resulting monoacetylated indoline (366) would then acetylate further giving compound (367).



Scheme 13

ii. Reaction with acetyl chloride:

When spiro [(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one] (338) was treated with acetyl chloride at room temperature it failed to react. When this mixture was heated in dry benzene for several hours, a reddish solution was formed which on evaporation and crystallization yielded two compounds. Neither of these was found to be the N-acetyloxy derivative (349). A study of the properties and spectra of each compound indicated that one of them (the minor product) was an acetylated compound while the other (the major product) was a chlorinated derivative.

The mass spectrum (Fig. 5) of the acetylated product, $C_{19}H_{15}N_3O_3$, displayed a molecular ion (m/e 333) which expelled a ketene molecule as expected from an acetate. Its i.r. spectrum showed two carbonyl bands at 1688 and 1712 cm^{-1} and was devoid of OH and NH absorption (?). The dark-red color of this product was indicative of conjugation; this was also shown by the absence of the methylene signal in its n.m.r. spectrum which showed two methyl signals at δ2.44 and 2.48, an eight-proton aromatic multiplet between δ7.0 and 8.2 and a one-proton doublet centered at δ9.8 (J=8 Hz).

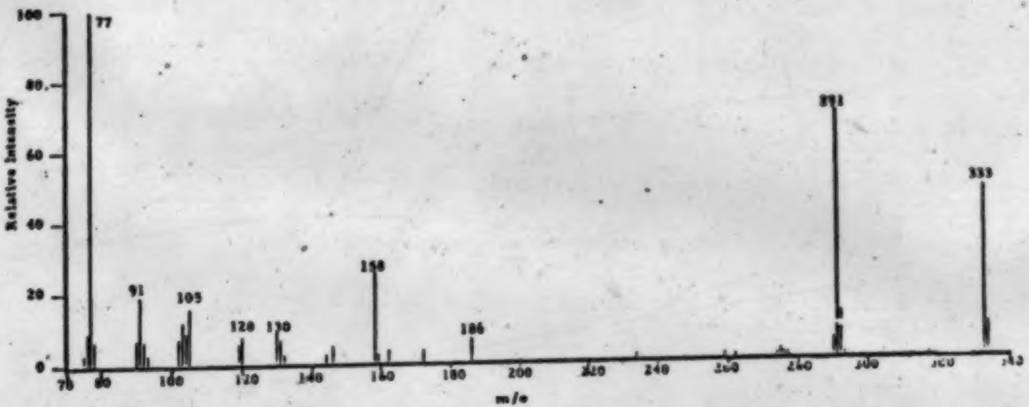


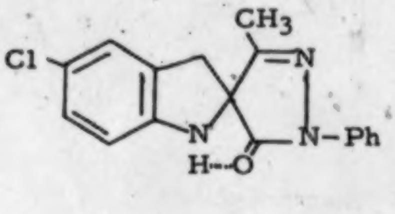
Fig. 5: A portion of the mass spectrum of an unidentified acetylation product, M^+=333.

This acetylated compound hydrolyzed readily in the presence of alkali giving a yellowish product which analyzed for $C_{17}H_{13}N_3O_2$ (M^+= 291). The presence of a phenolic function in this deacetylated product was suggested by its solubility in dilute alkali solution and by the broad absorption between 2000 and 3300 cm^{-1} in its i.r. spectrum. The n.m.r. spectrum (DMSO-d_6) displayed a very broad signal around δ4.6 and in addition, a methyl signal at δ2.58, an aromatic multiplet (8 protons) and a one proton doublet centered at $\delta 8.5$.

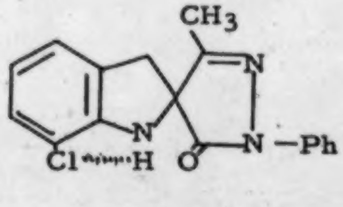
It is obvious that the product, $C_{19}H_{15}N_3O_3$, is an acetylated phenol. However, no structure can be suggested which satisfies all the data which accumulated for this compound. In particular, the one-proton doublet in the n.m.r. spectra of both the acetylated and hydrolyzed products seems strange and hard to rationalize. That an N-acetyloxy derivative might be formed first then rearranged is a possibility, but when a sample of the N-acetyloxyindoline (349) prepared earlier was refluxed in benzene it gave none of the above product. Instead, the dehydrated compound (A) and the 5-acetyloxyindoline (346d) were isolated.

The elemental analysis ($C_{17}H_{14}ClN_3O$) as well as the mass spectrum (M^+, m/e 311) of the major product confirmed the presence of a chlorine atom in its molecular formula. The possibility of this compound being the same 5-chloroindoline (346a) obtained earlier was ruled out by comparing i.r. and n.m.r. spectra and by the depression of a mixed melting point. However, the similarities of the spectral data of the product and that of (346a) suggested that both were isomeric. The n.m.r. spectrum was essentially similar to that of the 5-chloroindoline derivative (346a) except in the aromatic area where the substitution pattern differed. Again, this pattern was complex and could not be resolved. However, since one of these two isomers (346a) was proved to be substituted at the 5-position, it was considered likely that the isomer was a 7-chloro derivative (370).

These two position are more susceptible than any other position to attack by nucleophilic reagents. Accordingly, this product was tentatively identified as spiro [(7-chloroindoline)-2,4'-(3'-methyl-1'-1H-pyrazolin-5-one)] (370). Support for this conclusion was found in the i.r. spectrum of this compound which had an NH absorption band



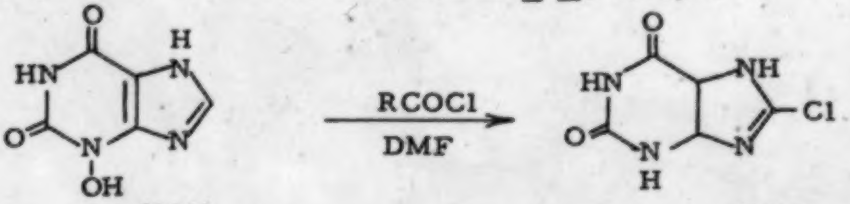
(346a)



(370)

at 3295 cm^{-1} and a C=O band at 1728 cm^{-1}. Compared to the corresponding absorption bands (3365 and 1710 cm^{-1}) in the related chloroindoline (346a), the N–H absorption showed a bathochromic shift of 70 cm^{-1} and the C=O a hypsochromic shift of 18 cm^{-1}. Intramolecular hydrogen bonding between the chlorine atom at C-7 and the amine hydrogen may be responsible for these shifts. In addition to the effect on the NH absorption, this also could affect the C=O absorption which is now located near the normal value (~1725 cm^{-1}) for compounds which do not display intramolecular hydrogen bonding. Hydrogen bonding between chlorine and hydrogen is now becoming universally accepted (Vinogradov and Linnell, 1971) and the large frequency shift demonstrated here for the NH absorption may indicate that chlorine is a stronger electron donor than oxygen in this molecule.

The formation of a chlorinated product as a result of treating the N-hydroxy compound (338) with acetyl chloride was not unexpected due to the availability, in the reaction mixture, of chloride ions for nucleophilic attack. Similar examples are reported with hydroxamic acids and heterocyclic N-oxides (Katritzky and Logowski, 1971d). The reaction, for example, between 3-hydroxyxanthine (371) and various acid chlorides, yielded only 8-chloroxanthine (372); no acyl products were obtained (Wölcke et al, 1969).

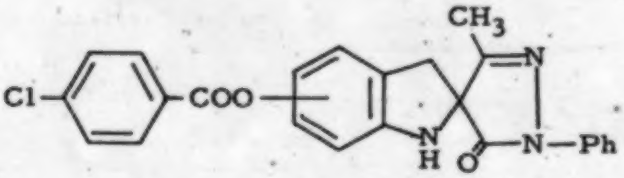


(371) (372)

At the moment, an explanation as to why a C-7 (370), and not a C-5 (346a) chlorinated product, was obtained in the reaction with acetyl chloride, is not possible although it may be in part due to the different solvents used (tetrahydrofuran for C-5 substitution and benzene for C-7 attack).

iii. Reaction with p-chlorobenzoyl chloride.

The reaction between the N-hydroxy compound (338) and p-chlorobenzoyl chloride was carried out under very mild conditions in an attempt to isolate the N-p-chlorobenzoyloxy derivative, but this proved unsuccessful. Although the i.r. spectrum of the crude product showed C=O absorption band at 1765 cm^{-1} which is indicative of N-benzoyloxy function (Kato et al, 1967; Zinner, 1958), crystallization of this product from cold ethanol resulted in skeletal rearrangement. The pure crystalline compound isolated analyzed for $C_{24}H_{18}ClN_3O_3$, as was expected for the N-benzoyloxy derivative, but its i.r. spectrum displayed an NH absorption band at 3380 cm^{-1} and two C=O bands at 1712 (lactam) and at 1732 cm^{-1} (benzoyl ester). The n.m.r. spectrum ($CDCl_3$) showed a methyl signal at δ2.15, a methylene doublet of doublets centered at δ3.45 (J=17 Hz), an aromatic multiplet (12 protons) and a D-exchangeable one-proton signal at δ 4.47 (NH). These data indicated that the benzoyloxy function rearranged to one of the ring carbons but the position of substitution on the benzene ring was not determined due to the complex nature of the aromatic signal in the n.m.r. spectrum. This compound is partly identified as spiro-[(x-p-chlorobenzoyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (373). Its mass spectrum supported this conclusion;



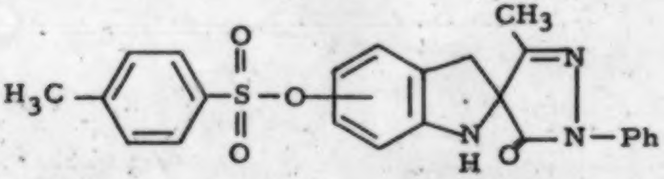
(373)

it displayed a molecular ion at m/e 431 which fragmented in a similar way to the other substituted indoline derivatives (see later). In addition, acyl-oxygen fission occurred with charge retention on the acyl portion (m/e 139); the latter fragmented further by the expulsion of a CO molecule.

An attempt to hydrolyse this benzoyl derivative to the corresponding phenol in order to help determine the position of substitution on the benzene ring failed to yield the required phenolic compound.

iv. Reaction with p-toluenesulfonyl chloride:

Treatment of the N-hydroxyindoline (338) with p-toluenesulfonyl chloride in pyridine gave a yellow solid. When this solid was dissolved in benzene, it deposited a crystalline compound which was found to be the dehydrated product (A) obtained when (338) was reacted with acetic anhydride (see p. 114). Evaporation of the remaining filtrate produced a solid residue which was chromatographed on a silica gel column, yielding two compounds. The major of these compounds was identified as the spiro-(5-chloroindoline)pyrazolone (346a) prepared earlier in this study. Direct comparison of the physical properties of both (346a) and the major isolated product established this identity. The minor product analyzed for $C_{24}H_{22}N_3O_4S$ and its mass spectrum displayed a molecular ion at m/e 447 which supports this formula. This, however, was not an N-tosyloxy derivative since the i.r. spectrum demonstrated a broad absorption band centered at 3340 cm^{-1} (NH). The n.m.r. spectrum also showed, in addition to the methyl, methylene and aromatic signal, a D-exchangeable one-proton signal at δ 5.0. These data suggested that the initially formed N-tosyloxy derivative rearranged to an isomeric tosylate which was assigned structure (374). The position of the tosylate group was not determined due to the complexity of the aromatic signal in the n.m.r. spectrum.



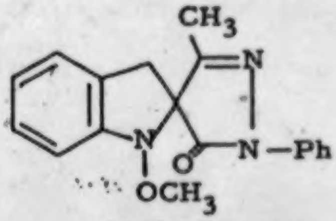
(374)

In another attempt to isolate an N-tosyloxy derivative, the reaction of (338) and tosyl chloride was performed in ether at 0°, in the presence of triethylamine. A black semisolid resulted which was shown by thin layer chromatography to contain at least five components. This was not investigated further.

f) Methylation:

An attempt to react the spiro (1-hydroxyindoline)pyrazolone

(338) with diazomethane, in the absence of any catalyst, failed to yield a methoxy derivative. When this reaction was carried out in methanol using boron trifluoride as catalyst, it produced a crystalline product which was found to be the 5-methoxyindole (346b). This compound resulted from an acid-catalyzed nucleophilic attack, by methanol, on the ring carbon. Accordingly, it was realized that this reaction should be performed in a medium free from alcohol. The reaction was repeated in dioxane and alcohol-free diazomethane and boron trifluoride-ether complex were used. This produced a dark-green product, the i.r. spectrum of which displayed a C=O absorption band at 1720 cm^{-1} but no OH or NH absorption. When this product was dissolved in cold ethanol, a high-melting solid (309°) slowly separated. This compound analyzed for $C_{17}H_{13}N_3O$ ($M^+ = 275$) and gave i.r. and mass spectra which were virtually identical to the dehydrated product (A) obtained when the N-acetyloxy compound (349) was treated with ethanol (see p. 114). A mixed melting point of both compounds showed no depression. The formation of this dehydrated product during crystallization of the crude product suggested that O-methylation did occur, then the methyloxy derivative decomposed and /or rearranged. Such a rearrangement could be catalyzed by traces of acid present with the crude product. Some support for this suggestion is the fact that it was possible to obtain the desired N-methoxyindoline (375) by methylating (338) with methyl iodide in the presence of sodium methoxide.



(375)

Identification of this compound was based on its elemental analysis ($C_{18}H_{17}N_3O_2$) as well as its i.r. (νC=O at 1719 cm^{-1}) and n.m.r. (N-OCH$_3$ at δ3.8) spectra. The mass spectrum of this compound (part IIIb) was also very informative; it displayed a molecular ion at m/e 307 and a strong $(M-31)^+$ ion resulting from the expulsion of a $CH_3O^{\cdot}$ radical from the molecular ion. The expulsion of this fragment is not normally observed in the mass spectra of methyl ethers unless an ortho-effect operates (Cable et al, 1972; Coutts and Malicky, 1973).

Other Reductions of 4-(2-Nitrobenzyl)-2-pyrazolin-5-ones (319a,b,c).

a. Reduction with iron and ferrous ammonium sulfate:

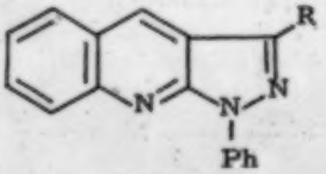
Aromatic nitro compounds are known to be readily reduced to amines by this reducing system (Hodgson and Hathaway, 1944; Hickinbottom, 1959). Reduction of the nitrobenzyl derivative (319b) using this method yielded the 4-(2-aminobenzyl)pyrazolone (321b). In contrast, reduction of the methyl analog (319a) was unpredictable. It sometimes gave the spiro-(N-hydroxyindoline)pyrazolone (338); on other occasions it yielded the 4-(2-aminobenzyl)pyrazolone (321a) or a mixture of both products. Varying the reduction time did not improve the situation. It is suggested that differences in the batches of iron used could account for these variable results.

b. Reduction with zinc and ammonium chloride:

This is generally a standard procedure for the reduction of aromatic amines to the corresponding hydroxylamines. Mousseron-Canet and Boca (1965) used this system to reduce some o-nitrobenzyl ketones to substituted 1-hydroxyindoles. When this reaction was performed with the 4-(2-nitrobenzyl)pyrazolone (319a), no N-hydroxy derivatives were obtained. The reaction yielded the spiro(indoline) pyrazolone (339) in poor yield. Reduction of the phenyl analog (319b) with the same reagent gave the corresponding spiro(indoline)pyrazolone (343) in good yield. In contrast, the 4(5-chloro-2-nitrobenzyl) pyrazolone (319c) gave a mixture of the spiro(5-chloroindoline)-pyrazolone (345a) and the corresponding N-hydroxyindoline (347).

c. Reduction with zinc and acetic acid:

Heating the nitrobenzyl derivative (319a) with zinc and acetic acid gave a dark yellow product which melted at 166-8° and proved difficult to purify. The i.r. spectrum lacked NH, OH and C=O absorption bands which suggested a pyrazoloquinoline derivative (376a). This suggestion was supported by the absence, in the n.m.r. spectrum of this compound, of any signals other than those of the methyl group and aromatic protons. Its mass spectrum displayed a molecular ion at m/e 259 which fragmented mainly by the expulsion of a hydrogen atom, a methyl radical and a methyl cyanide molecule (Scheme 14). A literature search revealed that this compound (376a) was known (m.p. 178°) having been prepared by heating the Schiff base of 4-formyl-3-methyl-1-phenylpyrazole and aniline (Brack, 1962).

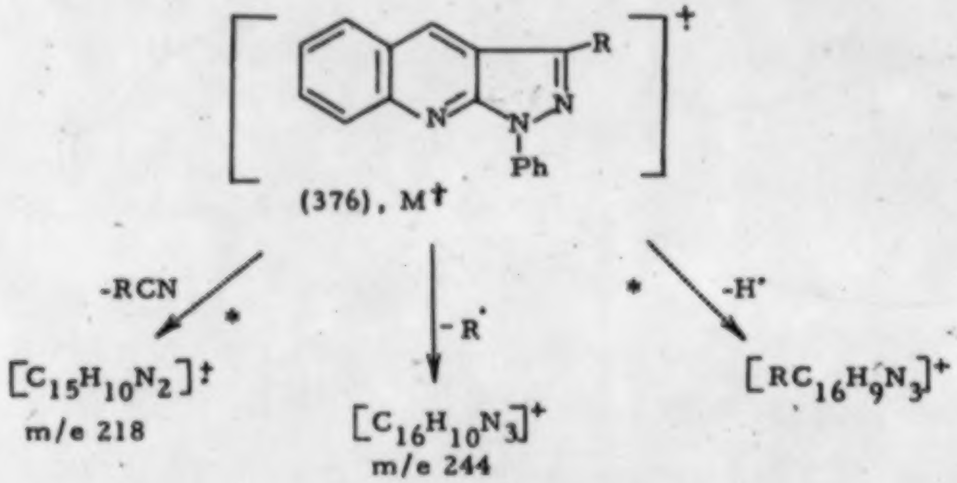


a, R=CH_3

b, R=Ph

(376)

When the phenyl analog (319b) was reduced with zinc and acetic acid, it yielded a pure yellow crystalline compound, $C_{22}H_{15}N_3$, which had i.r. and n.m.r. spectra very similar to those of (376a). The mass spectrum of this compound had a strong molecular ion of m/e 321 which was in agreement with the hitherto unknown structure (376b). Other than the molecular ion, this mass spectrum had only three ions of appreciable intensity resulting from the expulsion of a hydrogen atom, a phenyl radical and a phenyl cyanide molecule from the molecular ion (Scheme 14).



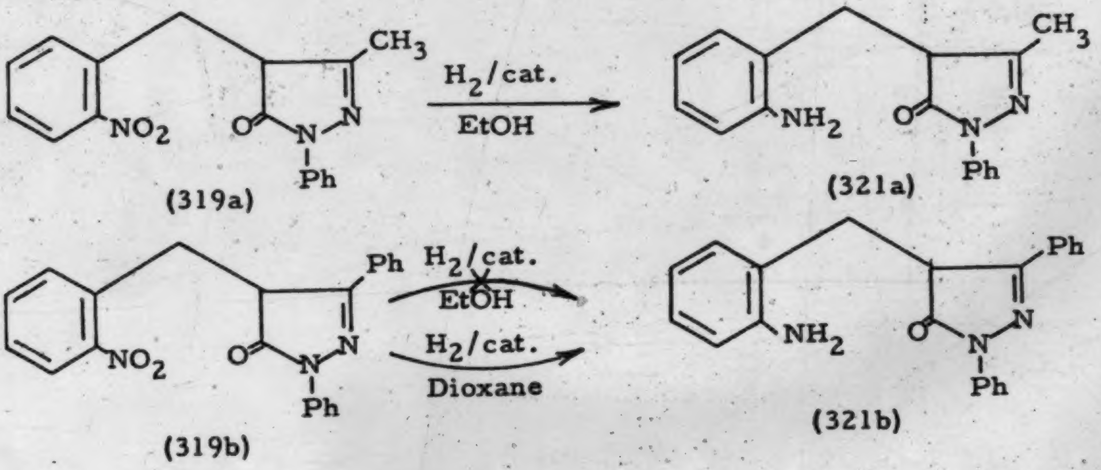
Scheme 14

Both these compounds (376a and b) were also obtained by heating the amines (321a, b) with acetic acid for several hours.

d. Catalytic hydrogenation: Preparation of some spiro-(tetrahydroquinoline)pyrazolones (337).

Catalytic hydrogenation of o-nitrobenzylpyrazolone derivatives (319a and b) was attempted to determine whether N-hydroxy compounds could be obtained by this route. During one of these trials, an interesting reaction was revealed. Catalytic reduction of two o-nitrobenzylpyrazolones (319a and b) was carried out using platinum oxide or palladium-charcoal as a catalyst and absolute ethanol as solvent. 1-Methyl-4-(2-aminobenzyl)-3-phenyl-2-pyrazolin-5-one

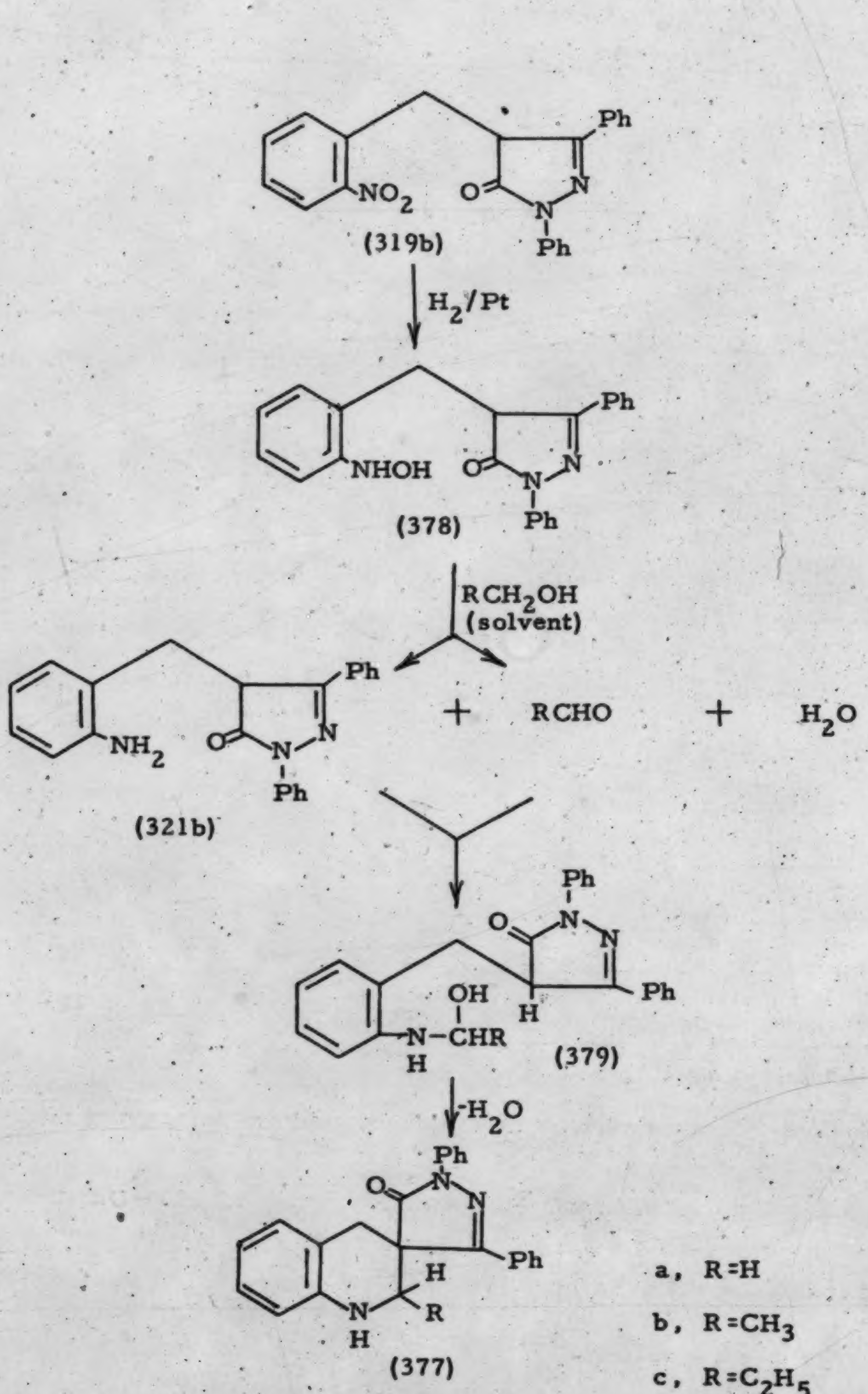
(321a) was the main product isolated from the reduction of the 3-methylpyrazolone (319a), but when the related 3-phenylpyrazolone (319b) was reduced under the same conditions, a different type of product was obtained. This product (designated compound B) was weakly basic and, unlike (321b), was insoluble in dilute sodium hydroxide solution.



Its i.r. spectrum had an NH absorption band at 3405 cm^{-1} and a C=O band at 1712 cm^{-1}. The presence of a carbonyl absorption at this frequency in addition to the lack of solubility of product (B) in dilute alkali solution, indicated that the pyrazolone ring was no longer capable of enolization i.e. the hydrogen atom α to the C=O group was no longer present. The n.m.r. of compound (B) included a 3-proton doublet centered at δ1.15 (J=6.5 Hz) and a one-proton quartet signal centered at δ3.6 (J=6.5 Hz). This n.m.r. evidence, therefore, revealed the presence of a $-\overset{|}{C}H-CH_3$ group in the product which apparently originated from the ethanol employed as the solvent in the catalytic reduction of (319b). To see if that was the case, the same reaction was repeated in dioxane, in methanol, in propanol and in benzyl alcohol. With dioxane, 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b) was obtained in good yield, but when the other solvents were employed, the products obtained in each case differed, and elemental analyses suggested that the alkyl or aryl group of the alcohol used had been incorporated into the molecule. The i.r. spectra of all these products were very similar but their nuclear magnetic resonance spectra confirmed differences in the structures of the products. The mass spectra of these derivatives were recorded and proved without doubt that the alcohols used as solvents were involved in this reaction.

From all these data, the general structure of compound (B) and the three related products was suspected to be the spiro-tetrahydroquinoline derivatives, spiro [(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-substituted-1',2',3',4'-tetrahydroquinolines)] (377). A mechanism for the formation of these spiro-tetrahydroquinolines (377) can be envisaged and is illustrated in Scheme 15. The nitro compound (319b) is reduced to the hydroxylamine (378) which then interacts with the alcohol present; the former is reduced to the amine (321b) while the latter is oxidized to the aldehyde. Both the amine and the aldehyde react to form a carbinolamine (or aldol) (379) which cyclizes to the tetrahydroquinoline derivatives (377). This suggested oxidation-reduction process, and subsequent interaction of the products, is another example of solvent/product interactions known to occur during catalytic hydrogenation (Pylander, 1967).

Some other structures for the unexpected reduction products were considered. Among these, the isomeric imines (Schiff bases) (380) had first consideration. It is known that aldehydes and ketones add to the primary amines, and this addition involves nucleophilic attack by the basic nitrogen at the carbonyl carbon atom


Ph
NO_2
O
N
N
Ph
(319b)
H_2/Pt
Ph
NHOH
O
N
N
Ph
(378)
RCH_2OH
(solvent)
Ph
NH_2
O
N
N
Ph
(321b)
+
RCHO
+
H_2O
Ph
O
N
N
OH
H
Ph
N–CHR
H
(379)
$-H_2O$
Ph
O
N
N
H
Ph
N
R
H
(377)

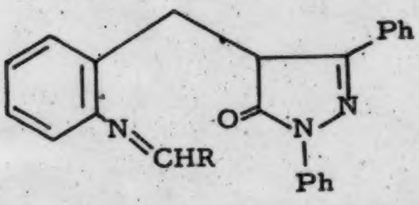
Scheme 15

a, R=H

b, $R=CH_3$

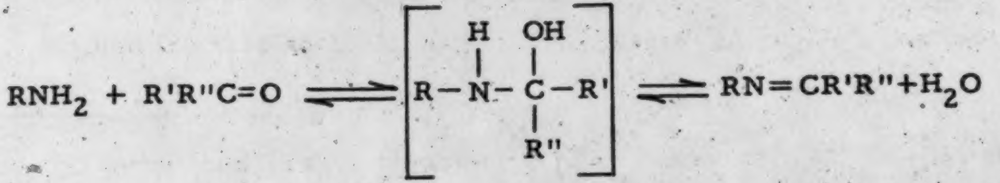
c, $R=C_2H_5$

d, R=Ph



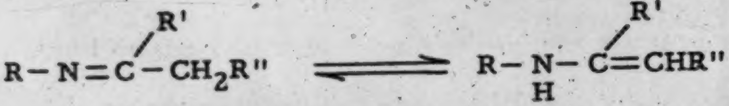
(380)

(equation 1). In most cases, the first step is the formation of an aldol



$$RNH_2 + R'R''C{=}O \rightleftharpoons \left[R-\overset{\displaystyle H}{\overset{|}{N}}-\underset{\underset{\displaystyle R''}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-R' \right] \rightleftharpoons RN{=}CR'R''+H_2O \quad (\underline{1})$$

or ketol, but in the majority of cases, the carbinolamine intermediate is unstable and not isolated. It reacts further in one of several ways, the most common of which is the elimination of water to give the imine. The possibility of compound (B) possessing an imine structure (380) was ruled out by an analysis of the i.r., n.m.r. and mass spectra as well as by the chemical properties of the product. The presence of N–H stretching bands in the i.r. spectra of all four compounds (377, R=H, CH_3, C_2H_5 and Ph) is incompatible with the imine structure. A broad deuterium-exchangeable signal in the n.m.r. spectrum was also observed. In imines, an NH absorption can be present if they exist in the enamine form (equation 2). Imines with α-hydrogens are

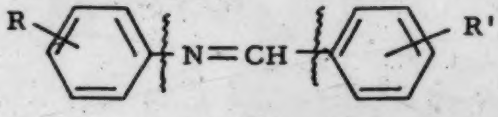


$$R-N{=}\overset{\displaystyle R'}{\overset{/}{C}}-CH_2R'' \rightleftharpoons R-\underset{\displaystyle H}{N}-\overset{\displaystyle R'}{\overset{/}{C}}{=}CHR'' \qquad (\underline{2})$$

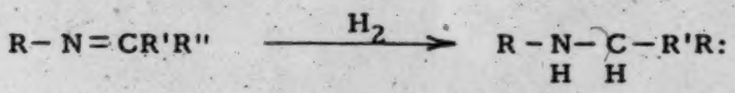
capable of imine-enamine isomerism similar to the keto-enol tautomerism of carbonyl compounds (Layer, 1963). This type of isomerism was clearly demonstrated in a number of cases, but Witkop (1956) found no evidence for the presence of the enamine structure in his i.r. studies. Conclusive evidence that the compounds obtained, when

(319b) was reduced in various solvents, did not have the imine structure came from a consideration of the product obtained by hydrogenation of (319b) in benzyl alcohol. This product gave rise to an NH stretching band in the i.r. spectrum despite the fact that it had no α-hydrogen capable of imine-enamine isomerization.

Further evidence for the suitability of structure (377) was obtained from an analysis of the mass spectra of the four compounds (377, R=H, CH_3, C_2H_5 and Ph). None of these fragmented under electron impact in the manner that Schiff bases do. Mass spectral studies of some Schiff bases have recently been reported by Elias and Gillis (1966). They showed that the molecular ion undergoes simple fission at the ring-nitrogen and ring-carbon bonds; the former fragmentation is more facile than the latter. No fragment ions due to ring-nitrogen fission were present in the mass spectra (Fig. 6 and 7) of any of the products isolated. On the other hand, the fragment pattern observed followed the behavior of tetrahydroquinoline derivatives under electron impact (Draper and MacLean, 1968) (Scheme 16, p. 148).

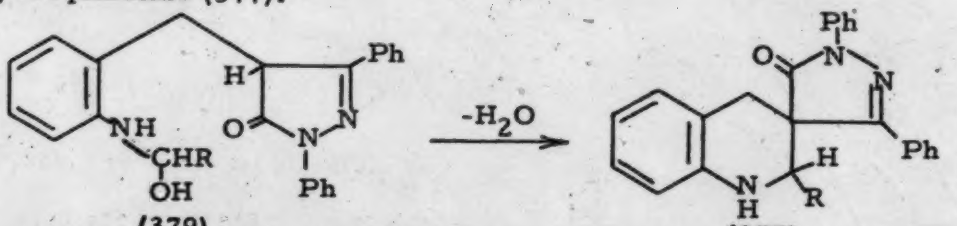


A final argument against the imine structure (380) was based on the fact that such a structure should not be isolated under such reduction conditions. Schiff bases are known to be reduced in virtually quantitative yields either by catalytic hydrogenation or by chemical reagents (Adkins, 1937), and accordingly, the imine if it were formed would be reduced to the secondary amine (equation 3).



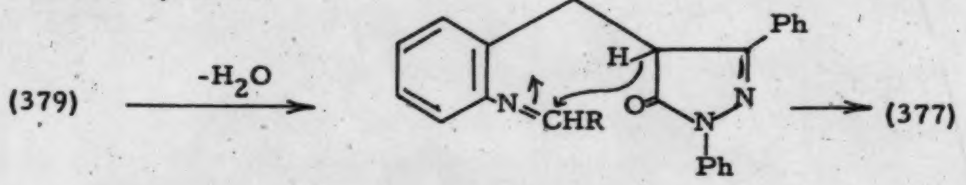
$$R-N=CR'R'' \xrightarrow{H_2} R-\underset{H}{N}-\underset{H}{C}-R'R: \qquad (\underline{3})$$

However, the imine is thought to have a transitory existence in the formation of these tetrahydroquinoline derivatives (377). Two possible mechanisms can be suggested for the cyclization stage. It is possible that the aldol (379) dehydrates directly to give the tetrahydroquinoline (377):



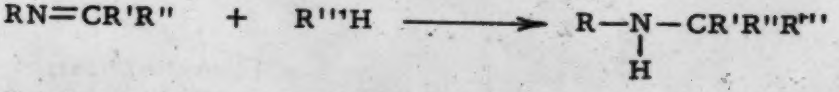
(379) (377)

Alternatively, the aldol could dehydrate to form the Schiff base (380) which then cyclizes:



(380)

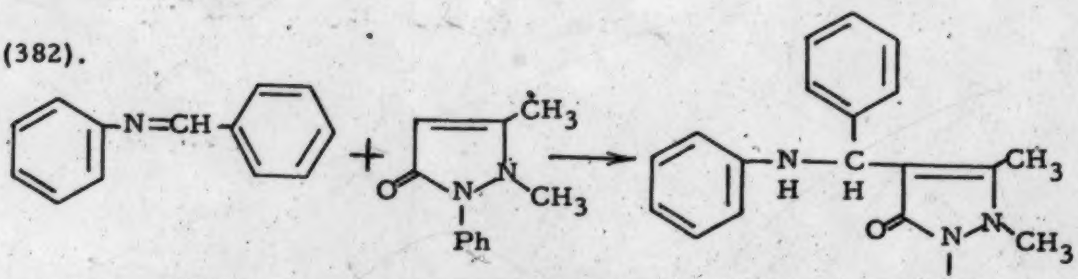
The Schiff base intermediate mechanism is supported by the fact that numerous compounds containing active hydrogens are known to add readily to the imines in the following manner:



$$RN{=}CR'R'' \quad + \quad R'''H \longrightarrow R{-}\underset{\displaystyle H}{\underset{|}{N}}{-}CR'R''R''' \qquad (\underline{4})$$

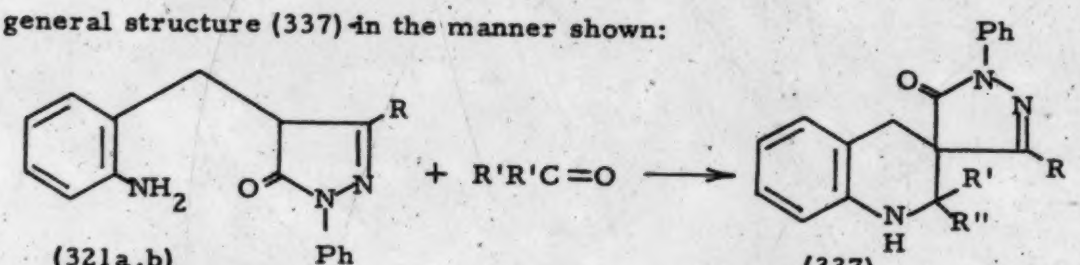
Catalysts such as aluminium chloride or cuprous chloride are often required in this reaction (Layer, 1963). The pyrazolone derivatives, 1-phenyl-2,3-dimethylpyrazolin-5-one (antipyrine) and 1-phenyl-3-methylpyrazolin-5-one are among the active hydrogen compounds reported to add to Schiff bases (Passerini and Ragni, 1936). This is due to the activity of the hydrogen atom at C-4 of the pyrazolone ring. Antipyrene (329) was found to add to N-benzylideneaniline (381) when both were dissolved in ethanol and left at room temperature for five weeks. The product isolated was identified as 4-benzalanilantipyrene

(382).



(381) (329) (382)

If the postulated mechanism depicted in Scheme 15 was factual, it should be possible to prepare numerous compounds of the general structure (337) in the manner shown:

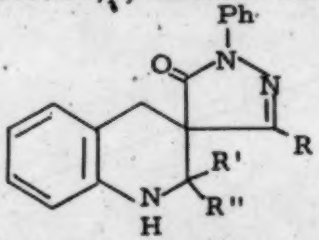


(321a,b) (337)

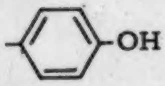
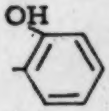
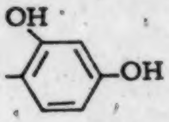
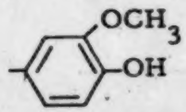
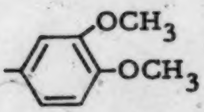
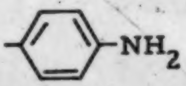
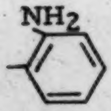
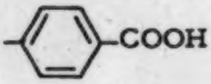
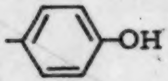
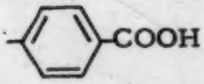
This proved possible. Eighteen spiro-tetrahydroquinoline derivatives (Table 2) were obtained from the amines (321a,b) and an appropriate aldehyde or ketone in refluxing ethanolic solution. The phenolic compounds (337d, e, f, g and o) and the carboxylic acid derivatives (337k and p) were prepared in particular because of their ability to dissolve in dilute alkaline solution, a property which was required to facilitate a planned pharmacological evaluation.

Aliphatic ketones are known to react with amines more slowly than aldehydes to form imines. This was the case here; it necessitated the use of higher reaction temperature and longer reaction times to obtain the tetrahydroquinoline derivatives (337q) and (337r) in the absence of catalyst or dehydrating agent. The reaction between (321a) and acetone required shorter reflux time when the solvent was butanol rather than ethanol. Attempts to crystallize the isolated product were unsuccessful but the i.r. and n.m.r. spectra of this

Table 2: Spiro(tetrahydroquinoline)pyrazolone derivatives.


Ph
O
N
N
R
R'
R"
N
H

(337)

	R	R'	R"
a	CH_3	H	CH_3
b	CH_3	H	C_2H_5
c	CH_3	H	Ph
d	CH_3	H	
e	CH_3	H	
f	CH_3	H	
g	CH_3	H	
h	CH_3	H	
i	CH_3	H	
j	CH_3	H	
k	CH_3	H	
l*	Ph	H	CH_3
m*	Ph	H	C_2H_5
n*	Ph	H	Ph
o	Ph	H	
p	Ph	H	
q	CH_3	CH_3	CH_3
r	Ph	CH_3	CH_3

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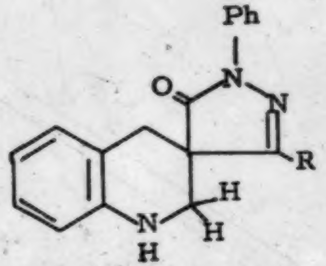
* These compounds are included in the table for completeness but are previously discussed under the identification numbers 377b, c and d.

product agreed with the proposed structure. The reaction between the phenyl analog (321b) and acetone was more facile and the product was easily characterized.

When the amines (321a, b) were reacted with formaldehyde, they failed to form the spiro-tetrahydroquinoline derivatives (383). The crystalline product obtained from heating (321b) with formaldehyde solution in ethanol analyzed incorrectly for the required compound. The i.r. spectrum of the product had a carbonyl band at 1711 cm^{-1} and no NH or OH absorption. It remains unidentified. The same reaction repeated with the methyl analog (321a) failed to yield any crystallizable products. The required spiro-tetrahydroquinolines (383) were readily obtained, however, when the nitro compounds (319a, b) were catalytically hydrogenated over platinum using methanol as a solvent.



(383)

a, R=CH_3

b, R=Ph

As a result of the successful formation of the tetrahydroquinoline (383a) by catalytic hydrogenation of (319a) in methanol, the same reduction in ethanol was reinvestigated. It was found earlier that this reaction yielded only the amine (321a). However, leaving the reaction mixture for a further 24 hours at room temperature resulted in the formation of the tetrahydroquinoline (337a) along with the amine (321a). Separation of both compounds depended on the solubility of the latter in dilute sodium hydroxide solution. A mixture of the related tetrahydroquinoline (337b) and the amine (321a) was also obtained when the same reduction was repeated in propanol.

All the tetrahydroquinoline derivatives prepared in this study were identified by their correct elemental analysis and by the similarities between their i.r. and n.m.r. spectra and those described earlier for compounds (377a-d). The mass spectra of some of these derivatives were also recorded (Figs. 6 and 7) and some of the possible fragmentation pathways are suggested in Scheme 16. Deuteration of compound (337c) as well as recording of the spectrum of the 2,2-dimethyltetrahydroquinoline (337r) were helpful in accounting for the origin of some of the fragment ions. Each compound demonstrated a strong molecular ion which was, in most cases, the strongest in the spectrum. The expulsion of a hydrogen atom as well as the substituent (R') in the form of a radical from C-2 of the tetrahydroquinoline ring gave rise to weak fragment ions. Exceptions to that are those compounds having no substituents at C-2 (383, R'=H) and those having aliphatic substituents (383, R'=CH_3 or C_2H_5) where the (M-H) and (M-R') ions were found to be relatively strong. Deuterium labelling of (337c) showed that the hydrogen atom expelled in the formation of ion a did not originate from the N-1 position of the tetrahydroquinoline ring. The absence of this ion a in the spectrum of the 2,2-dimethyltetrahydroquinoline (337r) suggested that the hydrogen atom at C-2 in the other compounds is the one involved.

An interesting fragment ion found in all the spectra (except the dimethyl derivative 337r) was due to the expulsion of an OH radical from the molecular ion. That this expulsion is direct was supported by metastable ions present at appropriate m/e values in most spectra. Deuterium labelling ruled out any contribution from the amine proton since the ion at m/e 450 in (337c) was located at m/e 451 in the deuterated compound. The absence of this ion in compound (337r) may suggest the involvement of the hydrogen atom at C-2 in the formation of the $(M-OH)^+$ fragment. However, without a detailed study it is not possible to make any deductions regarding the mechanism of OH loss. A similar fragment ion was detected in the spectra of the spiro-(indoline)pyrazolone derivatives (general structure 430) and a tentative mechanism for its formation was suggested in that instance (see Part III A).

Strong fragmentation ions (d and/or d') were present in the spectra of all compounds. These resulted at least in part, from the expulsion of a pyrazolone radical from the molecular ions as suggested by the presence of appropriate metastables. Depending on which hydrogen in involved in the expulsion of the pyrazolone radical, the two structures (d and d') are suggested for the ion formed. It seems, however, that the amine hydrogen is more involved in the proposed migration than the C_2-hydrogen. That was indicated by examining the spectra of both the deuterated compound (337c, N—D replaces N—H) and the 2,2-dimethyl derivative (337r). The former showed a major loss of 174 mass units from the molecular ion instead of 173 mass units lost in the non-deuterated compound (337c). The 2,2-dimethyl derivative (337r) molecular ion also expelled a pyrazolone radical (to give a fragment ion at m/e 146) thus implicating migration of the NH hydrogen atom, or alternatively, a hydrogen atom from the ring methylene group. Non-involvement of the protons at C-4 was

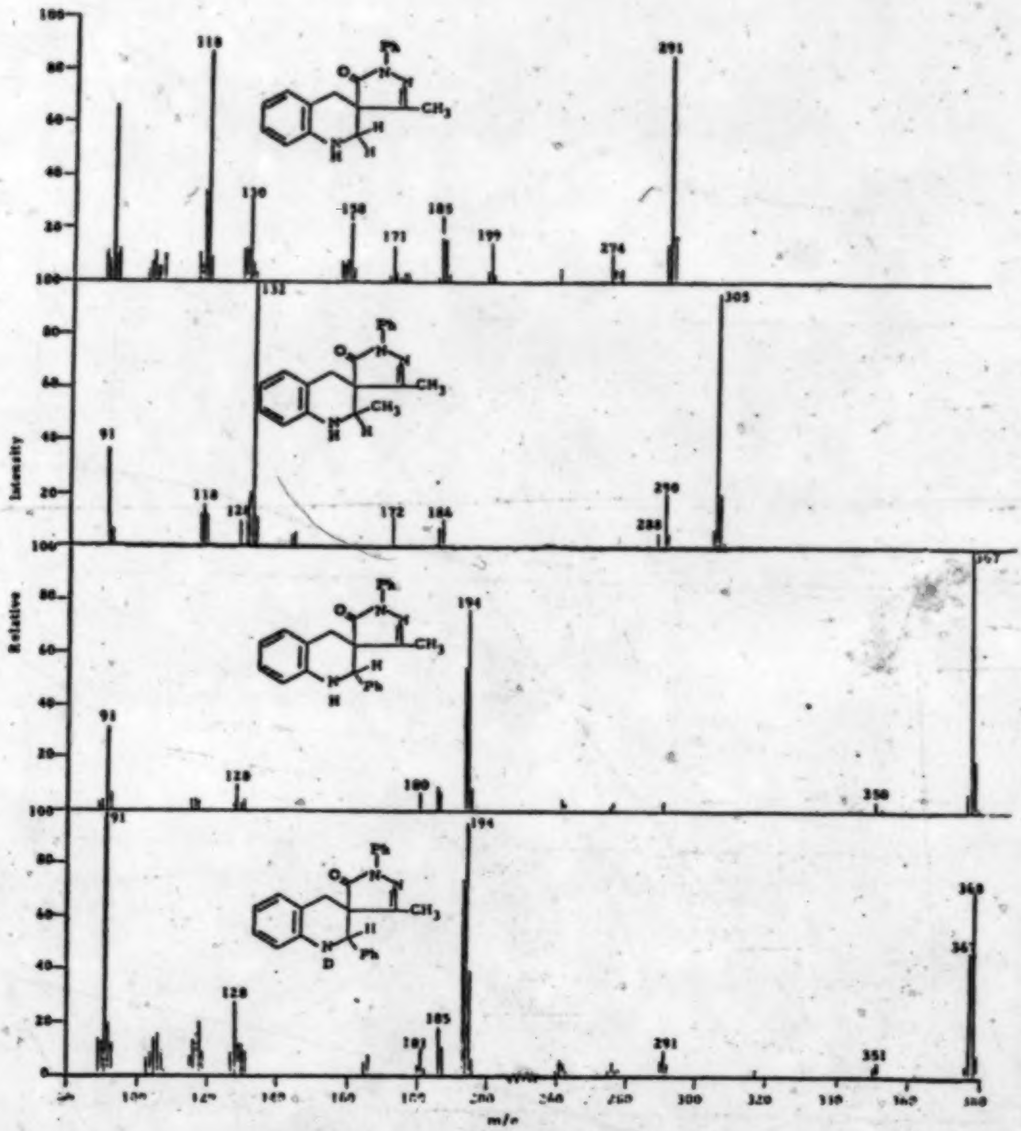


Fig. 6: Portions of the mass spectra of the spiro(tetrahydroquinoline) pyrazolones (383a, 337a, c) and the deuterated derivative of (337c).

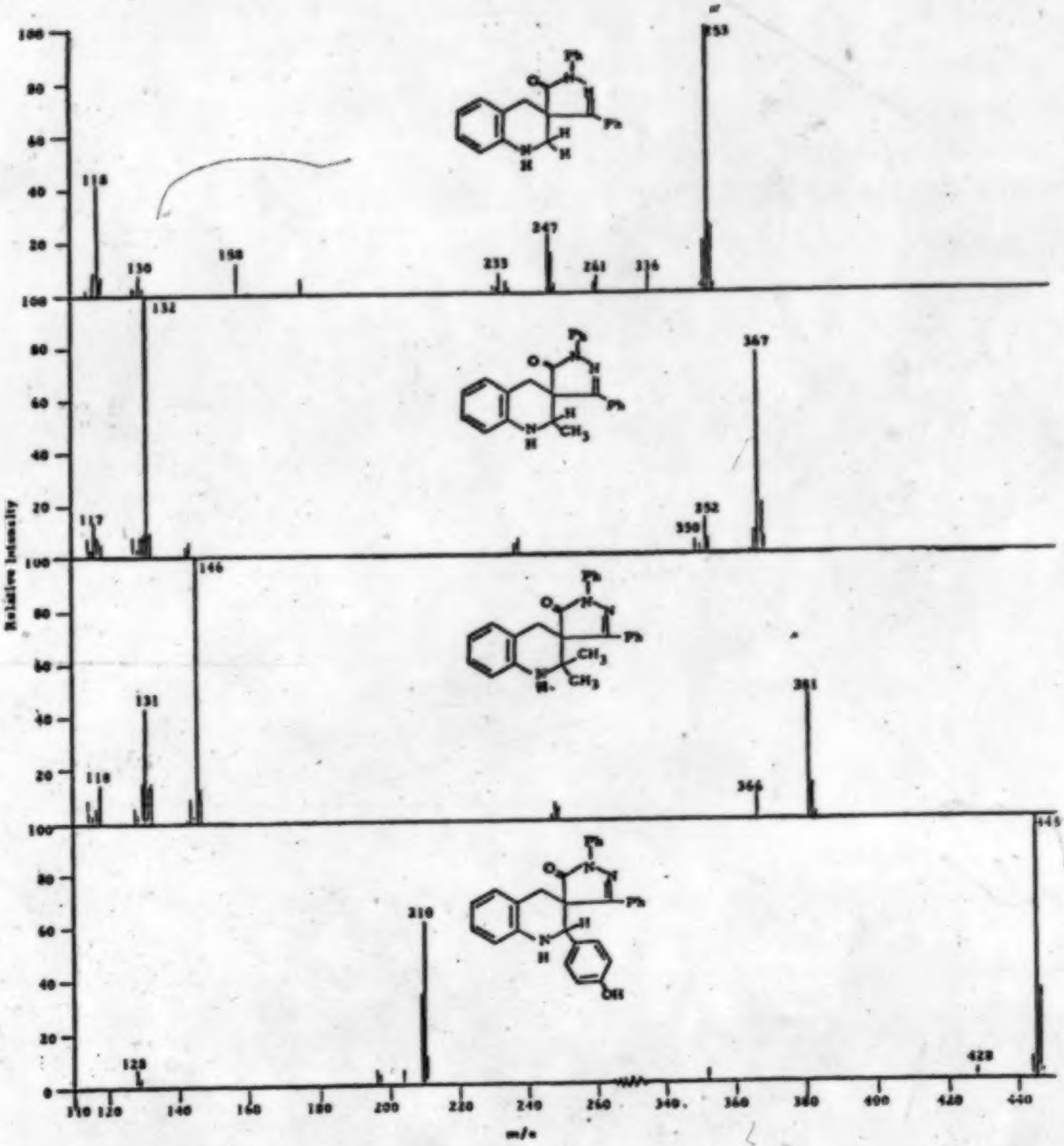
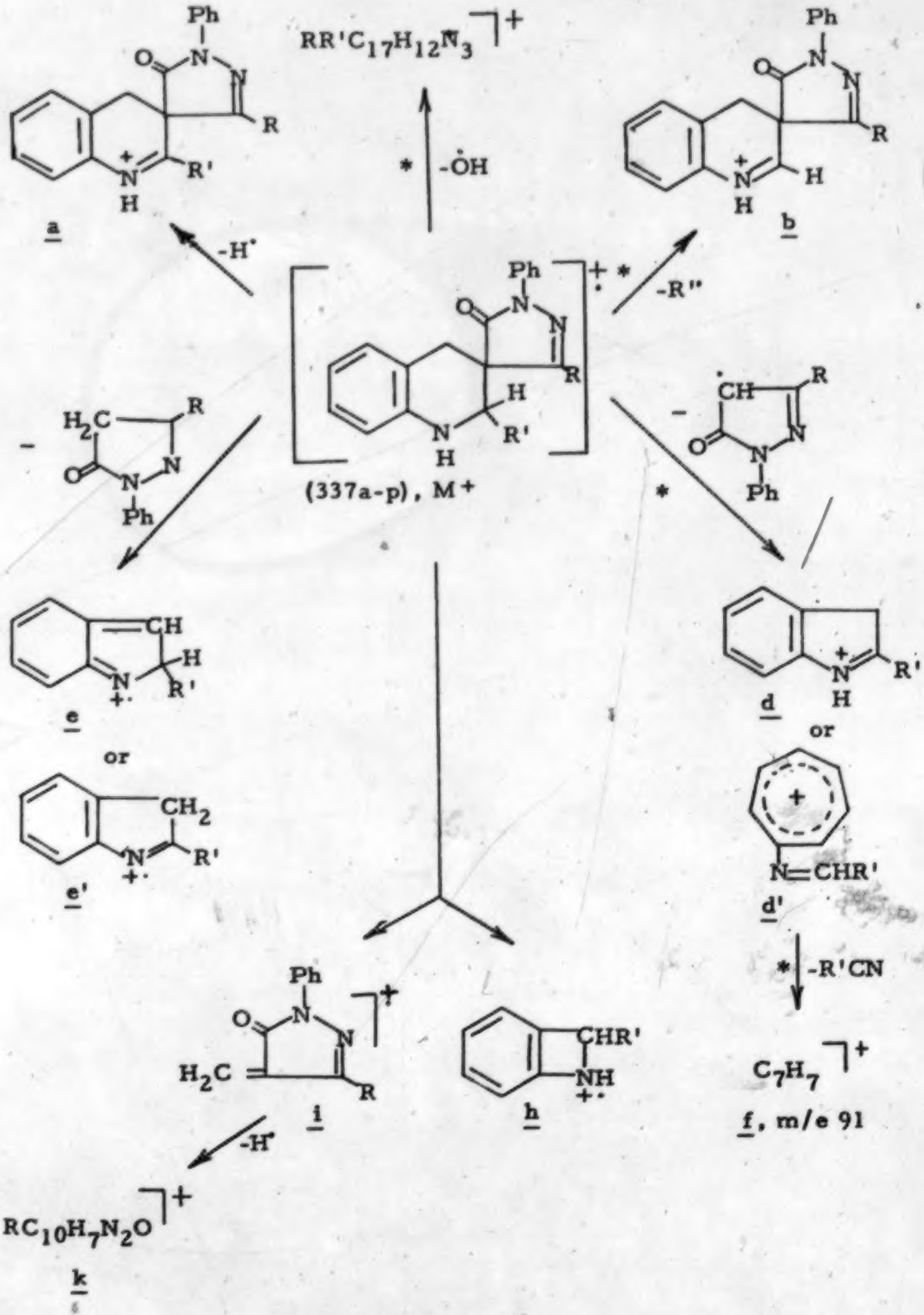
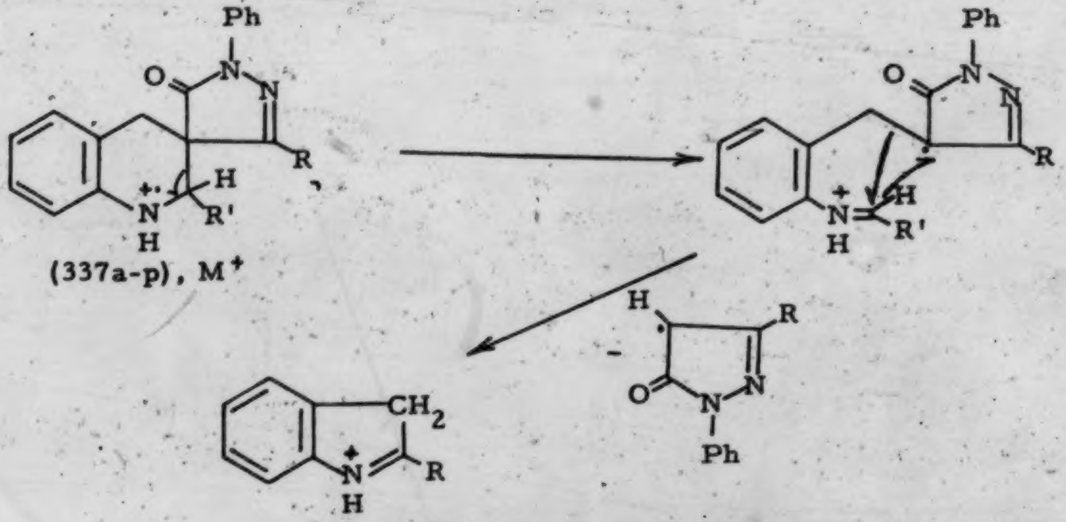


Fig. 7: Portions of the mass spectra of the spiro(tetrahydroquinoline)-pyrazolones (383b, 337l, r, o).

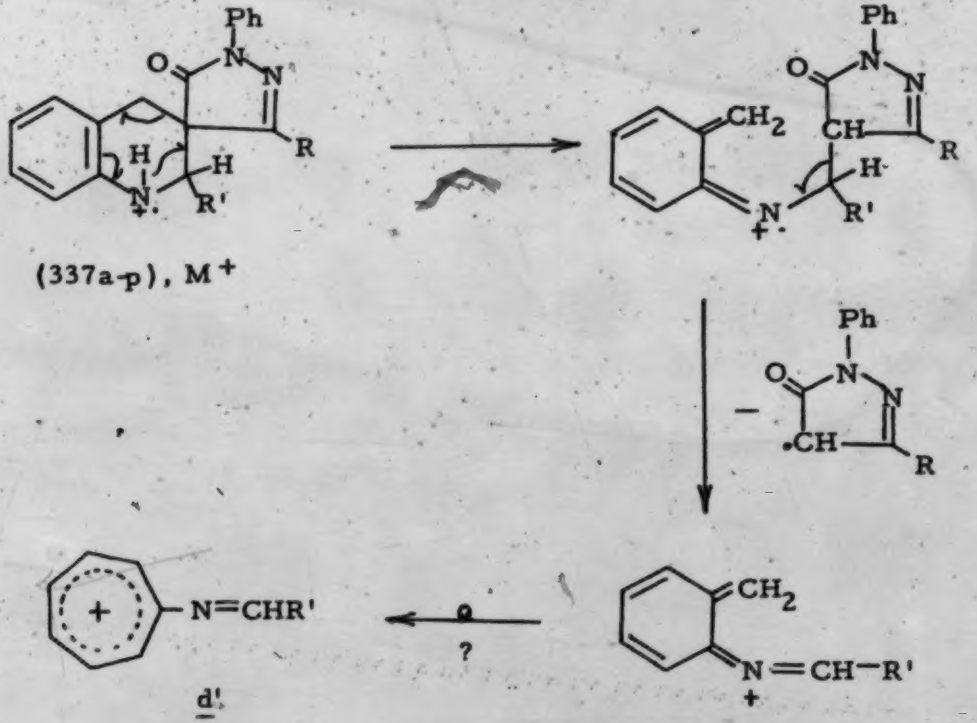

RR'$C_{17}H_{12}N_3$]+
* -ȮH
a
-H˙
b
-R''
(337a-p), M+
d
or
d'
* -R'CN
C_7H_7]+
f, m/e 91
e
or
e'
i
h
-H˙
$RC_{10}H_7N_2O$]+
k

Scheme 16

suggested, however, by the presence of similar strong ions (d and d') in the spectra of the spiro-dihydrobenzothiazines (see later) in which the methylene group is replaced by a sulfur atom. A mechanism for the formation of both ions d and d' is suggested in Schemes 17 and 18 respectively, but the latter is preferred for the reasons just expounded.


Ph
O
N
N
R
H
N
R'
H
(337a-p), M+
Ph
O
N
N
R
N
H
R'
H
H
R
−
O
N
N
Ph
CH2
N
R
H
d

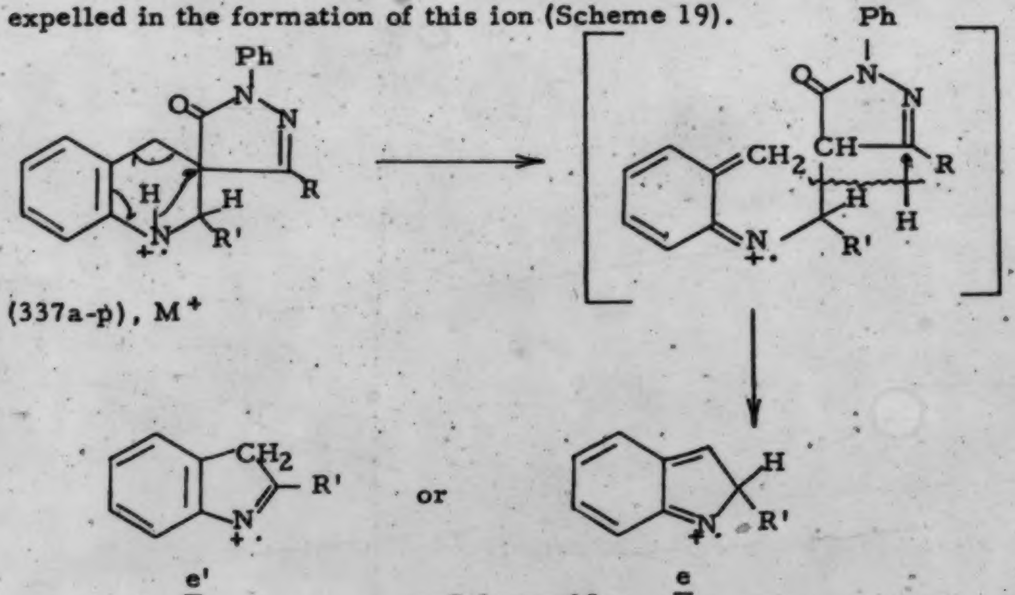
Scheme 17


Ph
O
N
N
R
H
H
N
R'
(337a-p), M+
Ph
O
N
N
CH2
CH
R
H
N
R'
Ph
O
N
N
−
•CH
R
CH2
N=CH−R'
+
N=CHR'
?
d'

Scheme 18

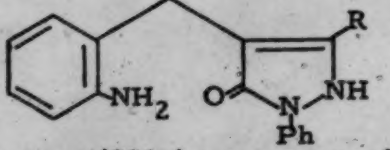
Another major pathway, especially in those tetrahydroquinolines which are not substituted at C-2, is the decomposition of the molecular ion in two ways to give ions tentatively identified as h and i. The latter expells a hydrogen atom to give ion k for which no structure is proposed.

Another ion, which is represented in Scheme 16 as e or e', is present in relatively high abundance in the tetrahydroquinolines possessing aromatic substituents at the C-2 position. The deuteration experiment confirmed that the amine hydrogen atom was the one expelled in the formation of this ion (Scheme 19).



Scheme 19

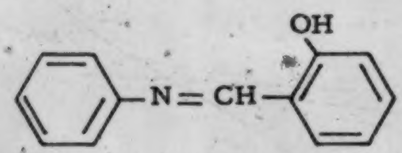
A difference between the o-aminobenzylpyrazolone (321a) and its phenyl analog (321b) was demonstrated in their reactions with



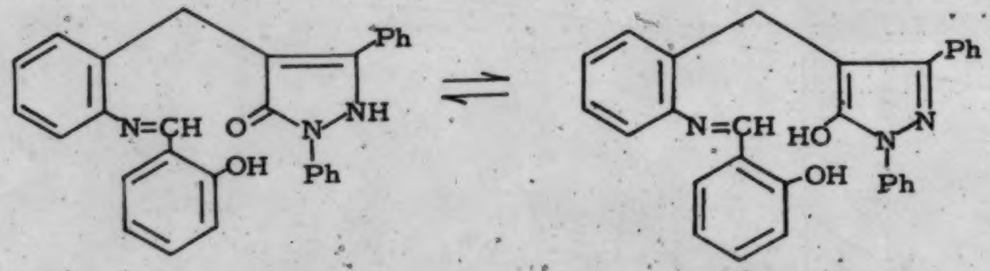
(321)

salicylaldehyde. Whereas (321a) was successfully converted to a spiro-tetrahydroquinoline (337e), the phenyl analog (321b) failed to produce such a structure. Instead, a yellow crystalline product

-designated as (C)- was obtained. It analyzed for $C_{29}H_{23}N_3O_2$ and had an i.r. spectrum which was devoid of both the lactam C=O and N—H absorptions present in all the spiro-tetrahydroquinolines (337). The spectrum contained a very broad absorption between 2100 and 3120 cm^{-1} in addition to four medium intensity bands at 1610, 1593, 1581 and 1568 cm^{-1}. These absorptions are comparable to those in the i.r. spectrum of the Schiff base, salicylideneaniline (384) which was prepared for comparison purposes. Accordingly, from these data, the Schiff base structure (385) is suggested for compound (C).



(384)



(385)

In addition to the elemental analysis and i.r. spectrum, the mass spectrum of (C) was also in agreement with the proposed structure. Although this spectrum (Fig. 8) displayed some similarities with the spectra of the spiro-tetrahydroquinoline (337e), it also showed strong fragment ions (Scheme 20) resulting from cleavage at ring nitrogen or ring carbon bonds of the imine group. Both these fissions were shown earlier (Elias and Gillis, 1966; Bowie et al, 1968) to occur in the mass spectra of Schiff bases. When product C was dissolved in DMSO-d_6 for an n.m.r. study, ring closure occurred.

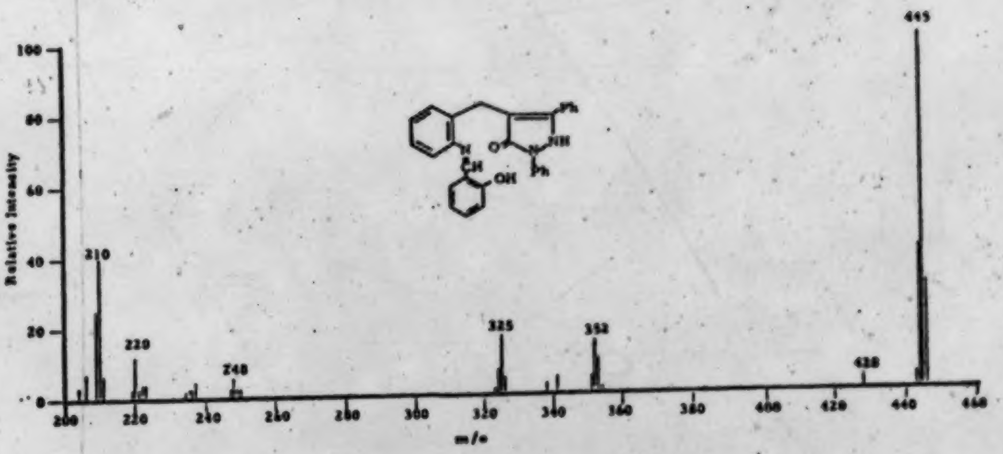
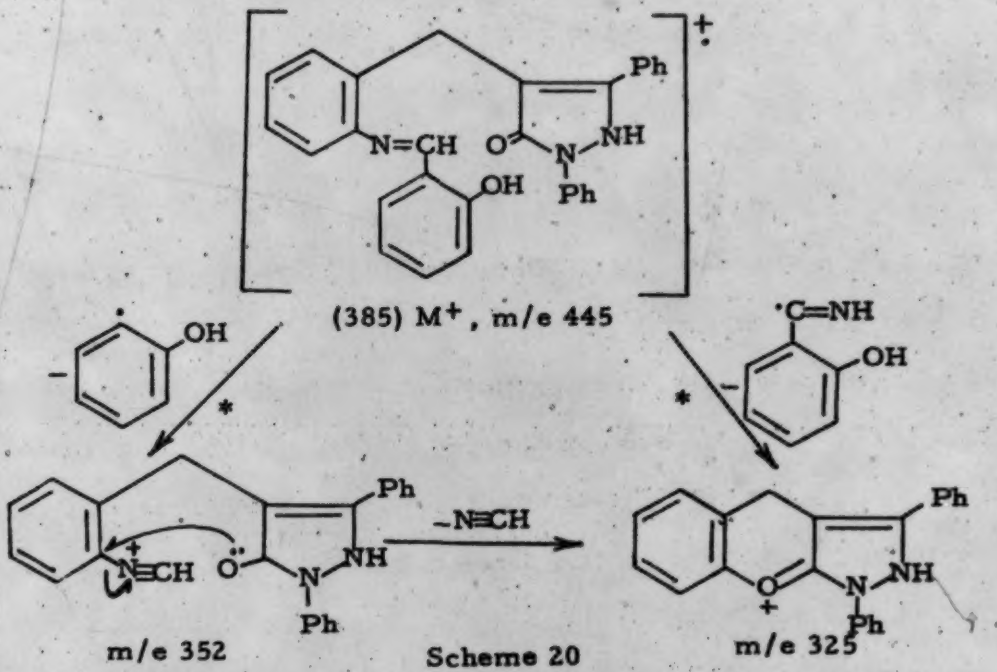
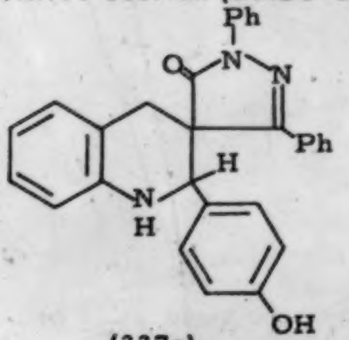


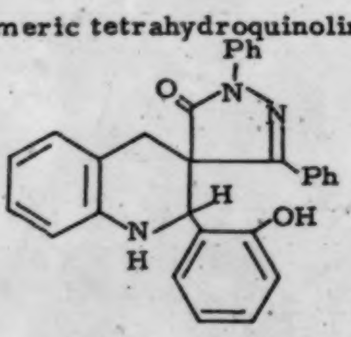
Fig. 8: A portion of the mass spectrum of 1,3-diphenyl-4-[2-(O-hydroxybenzylidene)aminobenzyl]-2-pyrazolin-5-one (385).


Ph
N=CH
O
NH
N
OH
Ph
(385) M+, m/e 445
OH
–
*
·C=NH
OH
*
–
Ph
N≡CH
O
NH
N
Ph
m/e 352
–N≡CH
Ph
O
+
N
NH
Ph
m/e 325

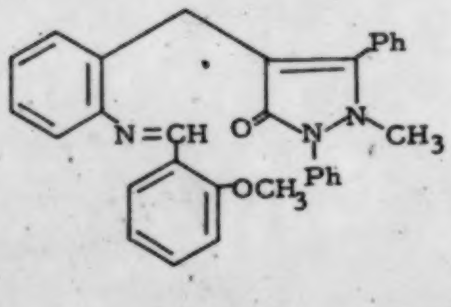
Scheme 20

A spectrum very similar to that of the spiro-tetrahydroquinoline (337o) was obtained. In particular, the spectrum of (C) displayed a doublet of doublets for the methylene group. Such a signal was demonstrated, throughout the present study, solely in spiro-compounds such as (337e). Compound (385), therefore, is converted in the n.m.r. solvent (DMSO-d_6) into the isomeric tetrahydroquinoline (386).


(337o)

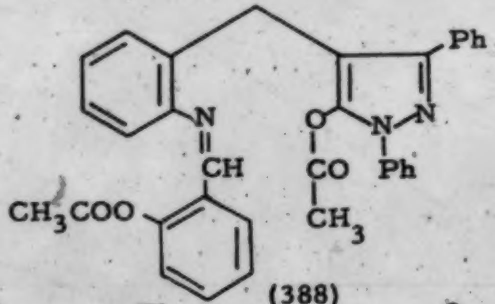

(386)

Reduction of (C) by means of sodium borohydride in aqueous dioxane did not yield any crystalline product. Also, methylation with dimethyl sulfate gave an alkali-insoluble product which was difficult to purify. The mass spectrum of the crude methylated product displayed a weak molecular ion at m/e 473 which indicated a dimethyl derivative in agreement with a Schiff base precursor (385) rather than a tetrahydroquinoline (386), since in (385), methylation of the pyrazolone nucleus, could also occur. As shown in the i.r. and mass spectra of the isolated products, methylation occurred at the N-2 position of the pyrazolone ring. The i.r. spectrum displayed a C=O at 1660 cm^{-1} which is expected only when the pyrazolone nucleus has an α,β-unsaturated carbonyl group (Nakanishi, 1962). The mass spectrum displayed, in addition to the M-1 and M-15 ions, a very strong ion (the strongest in the spectrum) at m/e 118. A similar ion was identified earlier (p. 89) in the mass spectrum of the N-2 methyl derivative (324b) as the fragment ($Ph-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow Ph-\overset{+}{C}=N-CH_3$). Accordingly, a structure (387) was assigned to the dimethyl derivative obtained from (C).

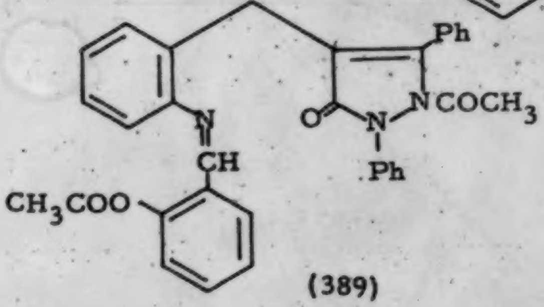


(387)

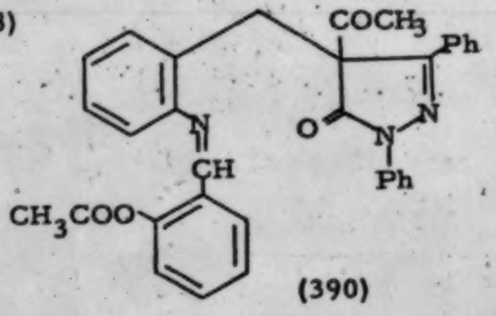
Acetylation of compound (C) with acetic anhydride produced a diacetate product (D) of molecular formula $C_{33}H_{27}N_3O_4$. Three diacetylated structures (388), (389) and (390) are possible. The O-5 position of the pyrazolone nucleus was found earlier to be most susceptible to acetylation by acetic anhydride. However,



(388)



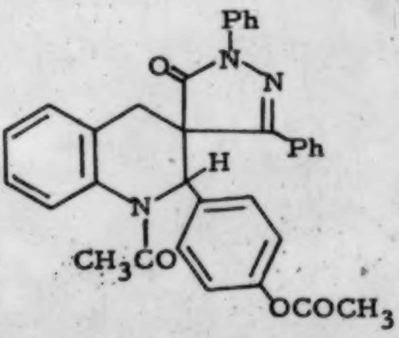
(389)



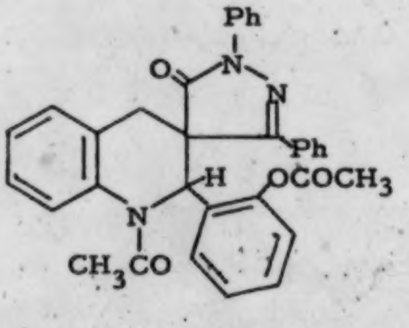
(390)

structure (388) was ruled out readily by examining the i.r. spectrum of (D) which contained three carbonyl bands at 1764, 1720 and 1666 cm^{-1}. Compound (388), if it was formed, would show only two ester carbonyl bands. The i.r. spectrum of (D) also disagreed with the acetylated compound being (389) which is not expected to show C=O absorption around 1720 cm^{-1}. Compound (390) is also a doubtful possibility since the C=O stretching band at 1666 cm^{-1} is relatively low for a ketonic carbonyl.

The similarities in the i.r. and n.m.r. spectra of the isolated product (D) and a diacetate derivative (391) obtained by acetylation of an authentic tetrahydroquinoline (337o) suggested two related structures. The i.r. spectrum of (391) had three C=O absorption bands at 1765 (ester), 1715 (lactam) and 1668 cm^{-1} (cyclic amide) which are closely related to those in the i.r. spectrum of (D).



(391)

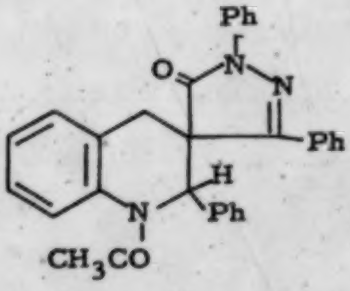


(392)

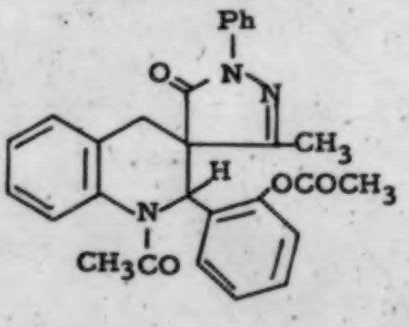
The n.m.r. spectrum of (391) displayed two methyl signals at δ 2.1 ($OCOCH_3$) and at δ 2.23 ($NCOCH_3$), a doublet of doublets centered at δ 3.37 (CH_2) and an aromatic multiplet which included the C-2 proton signal. The corresponding signals in (D) were located at δ 1.93, 2.24 and 3.26. These spectral similarities led to the assignment of cyclic structure (392) for the diacetate product (D).

Reactions of spiro-(tetrahydroquinoline)pyrazolones

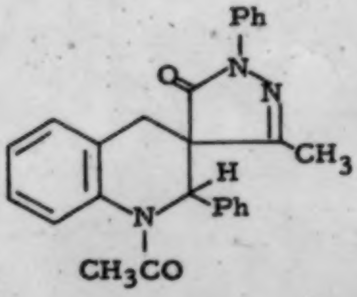
(a) Acetylations: Acetylation of some other tetrahydroquinolines were attempted initially to compare the spectral characteristics of the products with those of compound D. The tetrahydroquinoline (337n) yielded a monoacetyl derivative identified as (393). This structure was confirmed by elemental analysis ($C_{31}H_{25}N_3O_2$), i.r. ($\nu_{C=O}$ at 1666 and 1720 cm^{-1}) and n.m.r. spectra. When the tetrahydroquinoline (337e) was acetylated, it yielded a diacetylated product identified as (394). It analyzed correctly for $C_{28}H_{25}N_3O_4$ and its i.r. spectrum showed three C=O absorption bands at 1766 (ester), 1700 (lactam) and 1670 (cyclic amide). The n.m.r. spectrum of this compound had three methyl signals at δ0.78, 1.86 and 2.18. The first of these signals was surprisingly far upfield, a position not expected for any of the methyl groups in compound (394). In order to assist in deciding its origin, the acetyl derivatives (395) and (396) were prepared. The results are summarized in Table 3 and indicate that it is the methyl


Ph
O
N
N
Ph
H
N
Ph
CH3CO

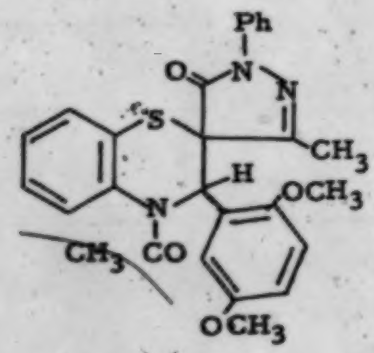
(393)


Ph
O
N
N
CH3
H
OCOCH3
N
CH3CO

(394)


Ph
O
N
N
CH3
H
N
Ph
CH3CO

(395)


Ph
O
N
N
S
CH3
H
OCH3
N
CH3 CO
OCH3

(396)

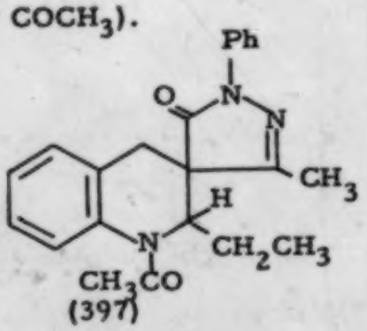
Table 3: The n.m.r. chemical shifts (relative to TMS) of the methyl and C_2–H signals in some acetyl derivatives of spiro-tetrahydroquinolines and spiro-dihydrobenzothiazines.

Compound	δ			
	$NCOCH_3$	$OCOCH_3$	$N{=}\overset{\vert}{C}{-}CH_3$	C_2–H
393	2.25	-	-	6.5
394	2.18	1.86	0.78	6.25
395	2.20	-	0.88	6.13
396	2.22	-	1.00	*
391	2.23	2.1	-	*
392	2.24	1.93	-	*
397	2.23	-	1.74	5.16
337b†	-	-	1.88	

* located within aromatic multiplet.

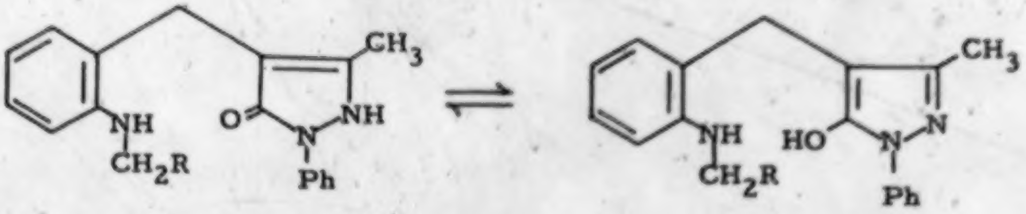
† is presented here for comparison

group on the pyrazolone ring which produces the upfield methyl signal in compound (394). A tentative explanation, based on the examination of Dreiding models, is that the $N{=}\overset{|}{C}{-}CH_3$ group is forced to align itself on top of the phenyl ring at C-2 of the tetrahydroquinoline ring or C-3 of the dihydrobenzothiazine ring and thus is greatly shielded. In addition, the hydrogen atom attached to the same carbon atom as the phenyl ring is forced into the plane of this phenyl ring, adopting "aromatic-like" character and therefore a downfield position. This explanation is supported by a study of the spectrum of the acetyl derivative (397) which lacks an aromatic substituent at C-2 of the tetrahydroquinoline ring. In the n.m.r. spectrum of this compound, the pyrazolone methyl signal came to resonance at δ1.74. This signal was found to be at δ1.88 in the non-acetylated tetrahydroquinoline (337b, i.e., 397, H for $COCH_3$).



(397)

(b) Reductions: Whereas sodium borohydride reduction of the imine (385) in aqueous dioxane gave no crystalline products, similar reductions of the isomeric spiro-tetrahydroquinolines (337a, b, c and d) yielded amphoteric products which analyzed for $C_{18}H_{18}N_3OR$. The ease of solubility of these products in aqueous sodium hydroxide suggested the presence of an enolizable hydrogen at C-4 of the pyrazolone nucleus. Structure (398) is suggested for the reduction products; this suggestion is supported by the spectral characteristics of these



(398 NH) (398 OH)

a, R=CH_3

b, R=C_2H_5

c, R=Ph

d, R=o-hydroxyphenyl

products. Their i.r. spectra displayed an N—H absorption band around 3300 cm^{-1}, lacked C=O absorption and showed broad absorption between 2100 and 3300 cm^{-1} which could be attributed to a bonded OH stretching band. The n.m.r. spectra of these products were very informative. In addition to the pyrazolone methyl signal and the aromatic signal, two deuterium-exchangeable protons and two methylene signals were also present. One methylene signal was a singlet while the other was a singlet or multiplet depending on the adjacent substituent (R). The mass spectra (Fig. 9) of the amphoteric products also supported the suggested structures (398). Some of the fragment ions in these spectra are tentatively identified in Scheme 21. The presence of ions a and b are of special interest since both contained an intact $NHCH_2R$ unit. Unlike compounds (398a) and (398b) which expelled the substituent (R) as a radical and gave fragment c, compound (398c, R=Ph) lacked this ion, but instead expelled a C_7H_7 radical to give an ion of medium intensity at m/e 278.

Reductions of the spiro-tetrahydroquinolines (337a, b

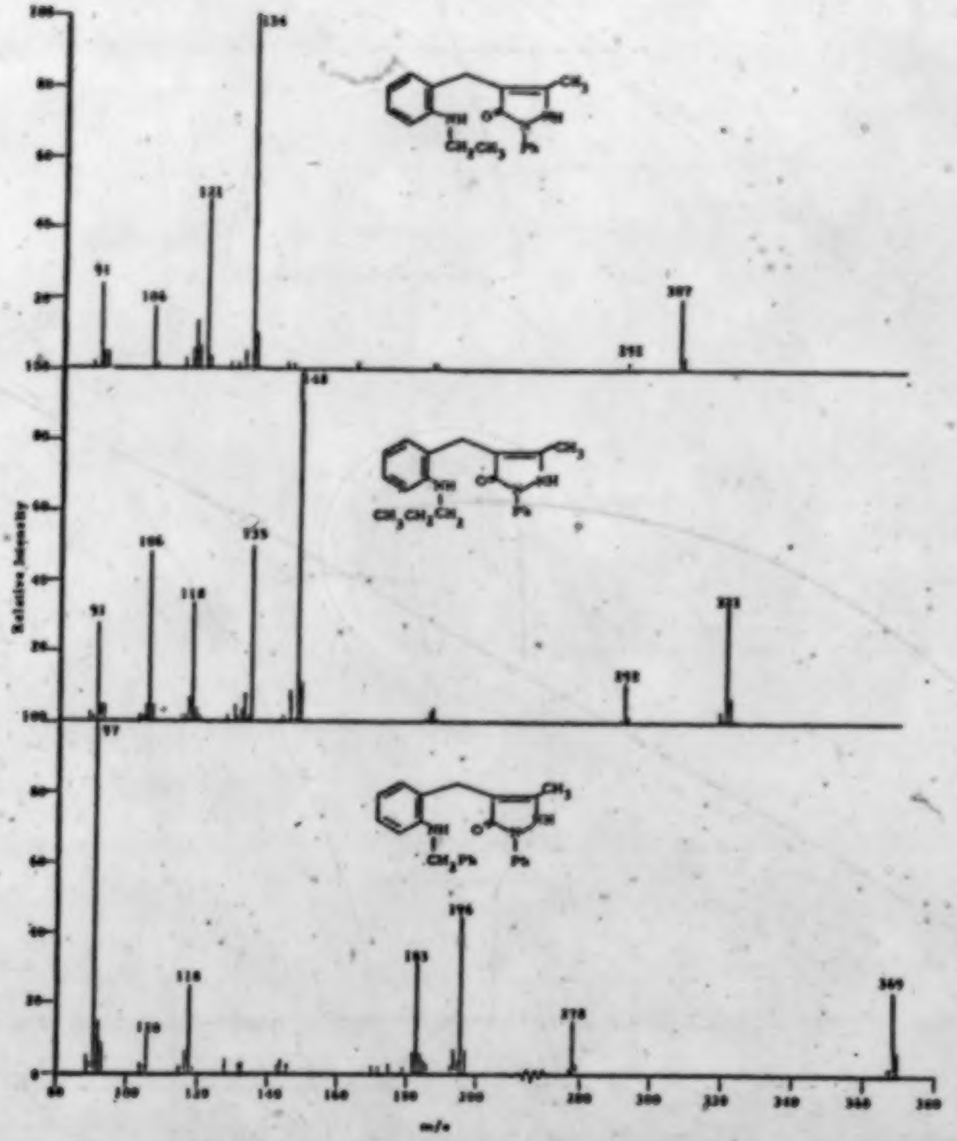
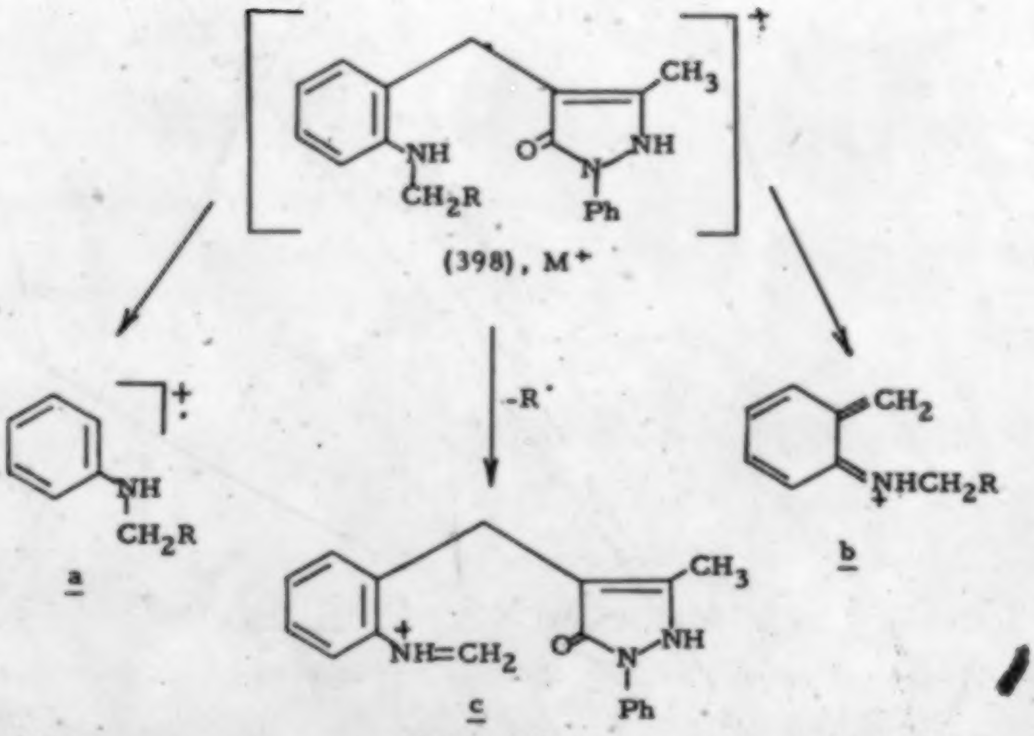


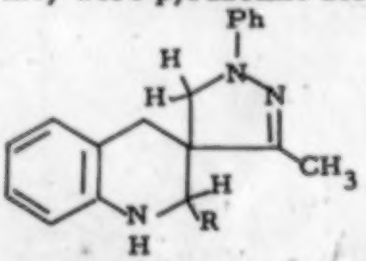
Fig. 9: Portions of the mass spectra of 4-(2-substituted aminobenzyl)-3-methyl-1-phenyl-3-pyrazolin-5-ones (398a, b, c).



Scheme 21

and c) were also performed using lithium aluminum hydride in ether. Two products were isolated from each reduction mixture, the minor product was basic while the major product was amphoteric. The proportion of these compounds was virtually reversed when the reduction of (337a) was carried out in tetrahydrofuran. In contrast, only the amphoteric product was obtained, when (337c) was reduced with lithium aluminum hydride/aluminum chloride in ether.

The amphoteric products were identical to the compounds obtained by sodium borohydride reduction of 337a, b and c, i.e. 398a, b and c respectively. The basic products analyzed for $C_{18}H_{18}N_3R$ (R=CH_3, C_2H_5 or Ph) and their mass spectra displayed molecular ions at appropriate m/e values for these formulae. This indicated that the lactam C=O groups were reduced by the action of lithium aluminum hydride, a reagent which is known to reduce pyrazolones to pyrazoline and pyrazolidine derivatives (Bowman and Franklin, 1957; Hinman et al, 1960; Bouchet et al, 1966; Elguero et al, 1971). The basic properties, the elemental analyses and the mass spectra of these products suggested that they were pyrazoline derivatives (399).



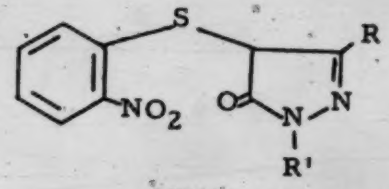
(399)

Their i.r. spectra lacked carbonyl absorptions. However, each had two absorption bands near 3400 cm^{-1} (sharp) and 3300 cm^{-1} (broad) which was somewhat puzzling since only one N—H stretching band was expected.

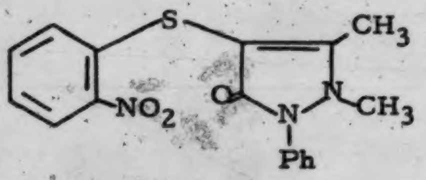
Part II: REDUCTIONS OF 4-(2-NITROPHENYLTHIO)-2-PYRAZOLIN-5-ONES.

Introduction:

A related investigation to the one discussed in part I is the study of the sodium borohydride/palladium-charcoal reduction of some 4-(2-nitrophenylthio)pyrazolin-5-ones to see whether cyclic N-hydroxy compounds could be obtained. The reduction of four of these derivatives (400 and 401) was initially performed by Pound (1970). Two products were obtained from the sodium borohydride/palladium-charcoal reduction of 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a). These were identified as 9,9a-dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo[4,3-b]-1,4-benzothiazine (402) and spiro [benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (403). The N-hydroxy compound (402) was reported to be readily oxidized in air to the spiro benzothiazoline derivative (403) and a mechanism for this transformation was



(400)

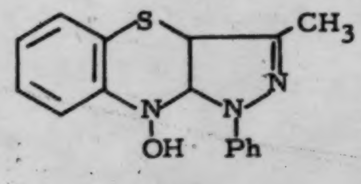


(401)

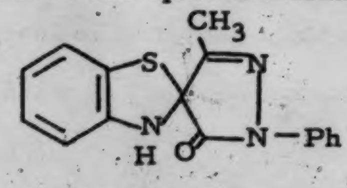
a, R = CH_3, R' = Ph

b, R = R' = Ph

c, R = CH_3, R' = H



(402)



(403)

suggested. Although the structure of the spirobenzothiazoline (403) is not in question, the structure of the proposed N-hydroxy compound (402) became doubtful for two reasons:

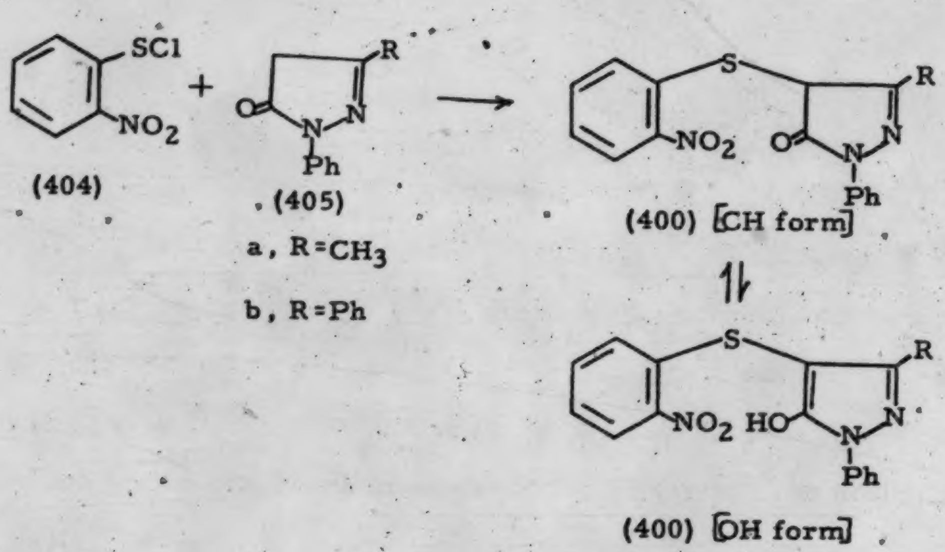
(a) The compound prepared by Pound (1970) was found to be amphoteric. An investigation of the properties of some cyclic N-hydroxy compounds described earlier in this thesis suggested that the N-hydroxy function in such a structure (402) would be neutral and therefore such a compound should be insoluble in alkali.

(b) The ease of conversion of the proposed N-hydroxy compound (402) to the spiro-benzothiazoline (403) suggested structural similarities, otherwise, a rather exotic rearrangement mechanism is required to explain this facile conversion.

For these two reasons, the reduction of two 4-(2-nitrophenylthio)-2-pyrazolin-5-ones was reinvestigated. These two compounds were 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a) and 4-(2-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (400b).

Preparation of two 4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-ones (400a,b).

Both compounds (400a) and 400b) were prepared by one of the methods reported by Coutts et al (1966). The condensation of o-nitrobenzenesulfenyl chloride (404) with 3-methyl-1-phenyl-2-pyrazolin-5-one (405a) in acetonitrile resulted in a good yield of 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a). Similarly, 4-(2-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (400b) was obtained by the reaction of o-nitrobenzenesulfenyl chloride (404) with 1,3-diphenyl-2-pyrazolin-5-one (405b).



(404) + (405) a, R=CH_3 b, R=Ph → (400) [CH form] ⇌ (400) [OH form]

Reductions of 3-methyl-4(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a).

Method (A): Use of sodium borohydride and palladium-charcoal in sodium hydroxide solution.

Because of its ability to enolize, this pyrazolone derivative is soluble in dilute alkalis. Accordingly, the sodium borohydride/palladium-charcoal reduction was carried out initially in 10% sodium hydroxide solution. On completion of the reaction, the filtrate was acidified with dilute acetic acid to yield a copious cream coloured product (E) which was readily soluble in 95% ethanol. On standing, however, a product precipitated from the solution. This compound, product (F), was no longer soluble in ethanol or most other organic solvents. Concentration of the mother liquor remaining after removal of product (F) led to the separation of variable yields of the previously identified spiro [(benzothiazoline-2',4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (403).

The elemental analyses of both products (E) and (F) indicated isomeric structures, $C_{16}H_{15}N_3OS$. The mass spectra of both were virtually identical and confirmed their molecular weights (297). The i.r. and n.m.r. spectra of both products were also identical. The ethanol-insoluble product (F) could be reconverted to product (E) by dissolving (F) in dilute sodium hydroxide solution and acidifying with dilute acetic acid. Because of this ease of interconversion, it was concluded that products (E) and (F) were diamorphic, although such a difference in solubility characteristics is difficult to explain.

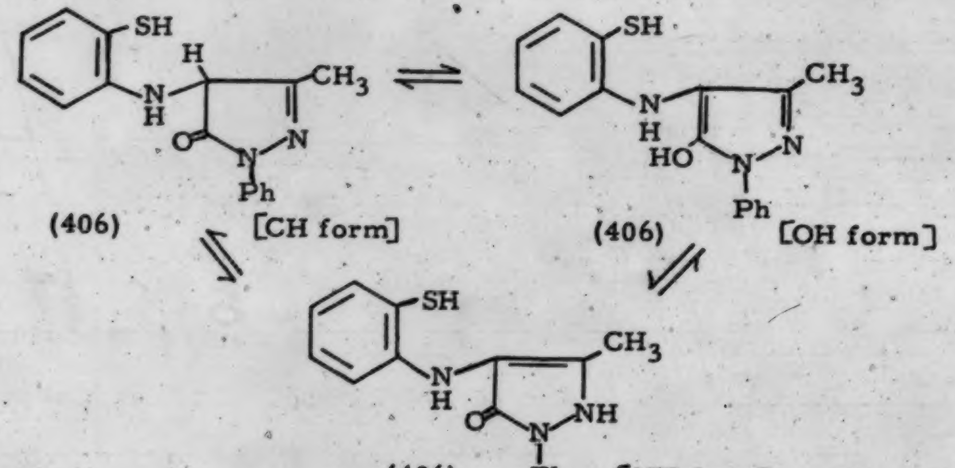
In order to identify the structure of this amphoteric product, the number of acidic groups in (F) was determined titrimetrically. The equivalent weight of this compound was found to be 148 which indicated that (F) possessed two acidic groups. The insolubility of this compound in sodium carbonate solution suggested that both the acidic groups were phenolic and/or enolic. At this point, it was possible to conclude that the proposed N-hydroxybenzothiazine structure (402) for product (F) was no longer valid.

Attempts were made to prepare chemical derivatives of (F) in order to help in positive identification. Although a pure acetylated derivative could not be prepared, it proved possible to isolate pure methyl and benzoyl derivatives. Methylation by means of dimethylsulfate in dilute sodium hydroxide solution produced a dimethyl derivative of (F) of molecular weight 325 (mass spectrum). Its i.r. spectrum showed a C=O absorption band at 1670 cm^{-1} in addition to an N—H stretching band at 3345 cm^{-1}. This indicated that product (F) also possessed a C=O group. The presence of an enolizable hydrogen at C-4 of the pyrazolone ring accounts for the apparent absence of C=O absorption in the i.r. spectrum of (F) [which, however, did have a medium intensity absorption band at 1626 cm^{-1} (bonded C=O?)] and also for its solubility in dilute alkali. The dimethyl derivative was no longer soluble in sodium hydroxide solution due to the absence of this enolizable hydrogen.

Benzoylation of product (F) was achieved by treating a cold sodium hydroxide solution of this product with benzoyl chloride. The elemental analysis ($C_{37}H_{27}N_3O_4S$) and the mass spectrum (M^+, m/e 609) of the resulting product revealed it was a tribenzoate. An accurate mass determination of the molecular ion was in agreement with this molecular formula.

Product (F) was also found to be very readily oxidized to compound (G) which Pound (1970) identified as the spiro(benzothiazoline)pyrazolone (403). Thus, when (F) was suspended in ethanol and the suspension exposed to the atmosphere, the compound first entered solution. On standing, however, yellow cyrstals identical with product (G) precipitated. The same occurred when (F) was dissolved in DMSO-d_6 in order to record its n.m.r. spectrum; a mixture of both compounds (F) and (G) was indicated by the spectrum. Another spectrum taken on the same sample after a few hours demonstrated only the presence of compound (G). This ease of oxidation of (F) to (G) indicated a similarity in both structures.

Based on all these findings, the structure of product (F) is concluded to be 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-pyrazolin-5-one (406). The absence of lactam C=O absorption in the i.r. spectrum of (406) suggests that the compound exists in the



(406) [CH form]

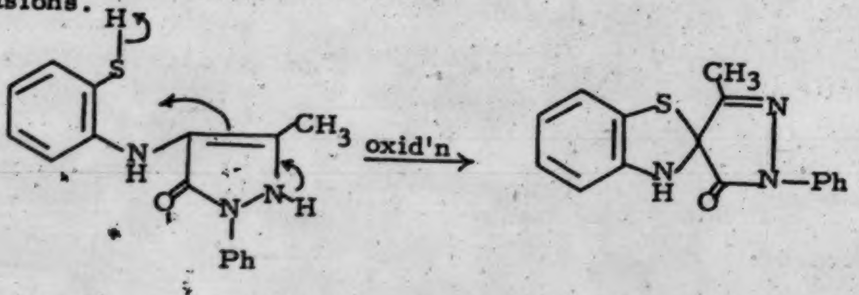
(406) [OH form]

(406) [NH form]

enolic form in the solid state. However, a closer look at the spectrum revealed the presence of a medium intensity absorption at 1626 cm^{-1}. This band could be due to a strongly bonded C=O absorption of the "NH" tautomer which is normally expected to be around 1670 cm^{-1} (Newman and Pauwels, 1969). The absence of a similar band in the i.r. spectrum of the diacetyl, dimethyl and tribenzoyl derivatives of (414) indicated that this assignment might be correct. Lack of solubility of compound (406) in most organic solvents and its ease of conversion to the spiro-benzothiazoline (403) hindered measuring the i.r. spectrum in solution. The absence of any C=O absorption close to 1700 cm^{-1} indicated the absence of any contribution from the "CH" form. The presence of a broad absorption band between 2400 and 3300 cm^{-1} masked the S–H stretching absorption which normally occurs as a sharp, easily recongnized band in the range 2550-2600 cm^{-1}, however, the weak maximum at 2600 cm^{-1} could be due to this absorption. The apparent lack of a stretching band for the thiol group earlier (Pound, 1970) led to the incorrect assignment of structure (402) to product (F). That the thiol function was present in (407) was clearly demonstrated in the mass spectrum (Fig.10) of this compound and was inferred from the i.r. and mass spectra of the diacetyl, dimethyl and tribenzoyl derivatives (see later).

The n.m.r. spectrum of compound (406) was measured immediately after dissolving it in DMSO-d_6, that is before oxidation could occur. It showed a three-proton signal at δ 2.05 which was attributed to the methyl group of the pyrazolone ring. The only other feature in the spectrum was the presence of a twelve proton multiplet between δ 6.3 and 8.0; two (or three) of these protons were exchangeable with deuterium. The signals of both the N–H and S–H protons as well as that of the pyrazolone ring proton are probably masked under this aromatic multiplet. Due to the adjacent nitrogen and sulfur atoms, the pyrazolone ring proton might be expected to appear downfield within the aromatic region. This suggestion is supported by the fact that no separate signals for the pyrazolone proton are detected in the n.m.r. spectra of the 4-(2-nitrophenylthio)-2-pyrazolin-5-one derivatives (400).

Elemental analysis, i.r. and n.m.r. data, therefore, are in agreement with the suggested structure (406) for the amphoteric product (F). This structure can also explain the ease of oxidation of product (F) to product (G) which was demonstrated on several occasions.



Product F (406)

Product G (403)

The mass spectrum of 3-methyl-4-(2-mercaptophenyl-amino)-1-phenyl-2-pyrazolin-5-one (406) is shown in Fig. 10 and its suggested fragmentation pathways are outlined in Scheme 22. The

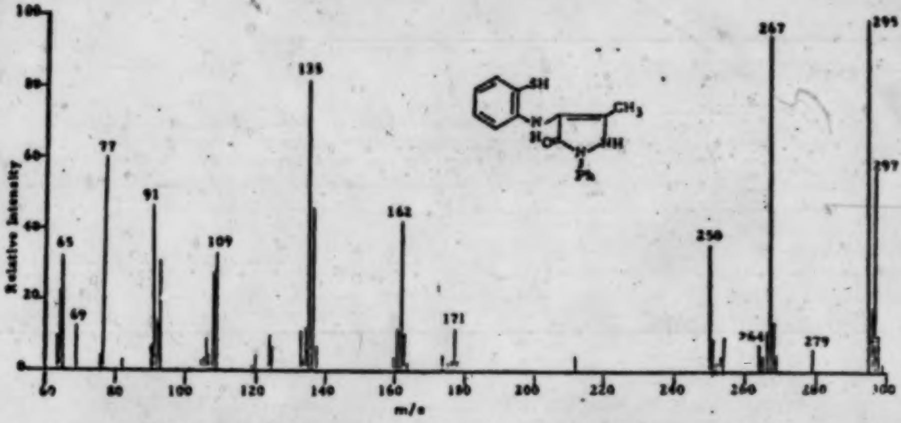
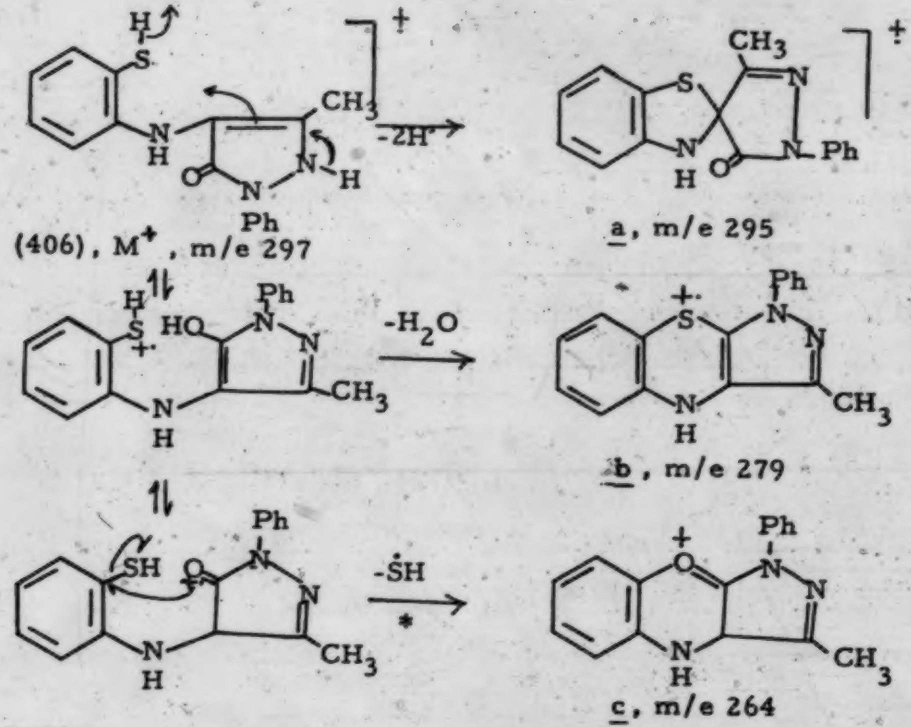


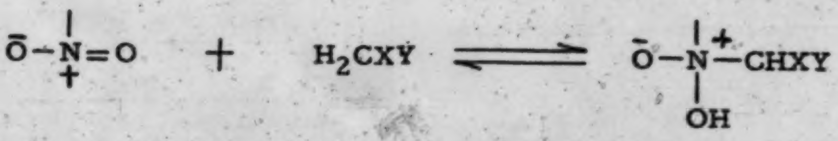
Fig. 10: A portion of the mass spectrum of 4-(2-mercaptophenyl-amino)-3-methyl-1-phenyl-3-pyrazolin-5-ones (398a, b, c).

major fragment (a) resulted from expulsion of a hydrogen molecule to give the spiro-benzothiazoline (403) and then followed the same fragmentation pattern of this compound; these will be discussed later in this thesis (part III A). Pound (1970) found that increasing the temperature of the probe or the length of time of bombardment resulted in increasing the intensity of the peak at m/e 295 which is the molecular ion of the spiro-benzothiazoline (403). It was suggested that rapid oxidation of compound (406) occurred in the probe of the spectrometer. Minor fragmentation pathways of compound (406) were very informative. These were the loss of an $\dot{S}H$ radical and a water molecule from the molecular ion; the first fragmentation was supported by the presence of a metastable ion. None of these fragments were found to be present in the mass spectrum of the spiro-benzothiazoline (403). Attempts to deuterate the amphoteric compound (406) were unsuccessful and resulted only in the formation of the deuterated spiro-benzothiazoline derivative (M^+, m/e 296).



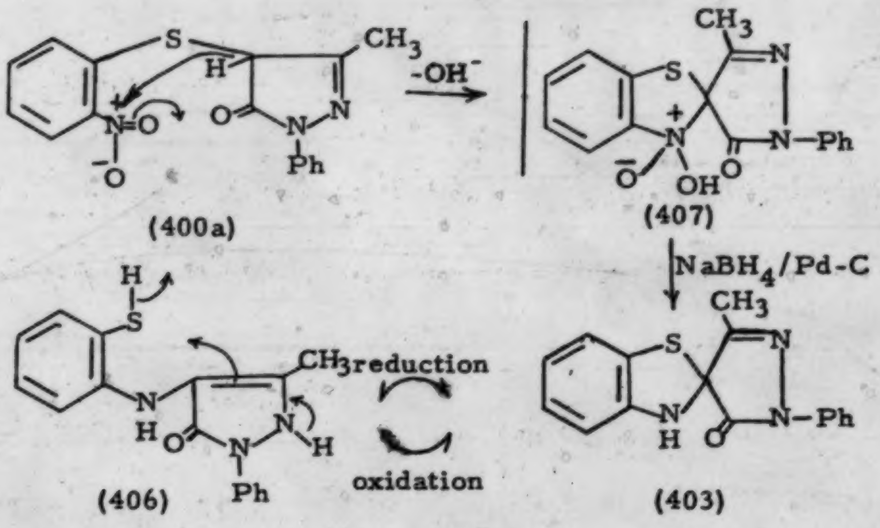
Scheme 22

A mechanism for the formation of the 4-(2-mercaptophenylamino)pyrazolone derivative (406) from the nitrophenylthiopyrazolone (400a) is suggested in Scheme 23. This is reminiscent of the work reviewed by Loudon and Tennant (1964) who considered that the nitro group can provide an electrophilic centre for additive reactions of the type exemplified by an aldol condensation:



$$\bar{O}-\overset{|}{\underset{+}{N}}=O \quad + \quad H_2CXY \rightleftharpoons \bar{O}-\overset{|\,+}{\underset{|\atop OH}{N}}-CHXY \qquad (5)$$

A similar intramolecular reaction can occur in the nitro compound (400a) between the active hydrogen at C-4 of the pyrazolone ring and the nitro group and this could lead to the heterocyclic intermediate (407). Reduction of (407) would result in the formation of the



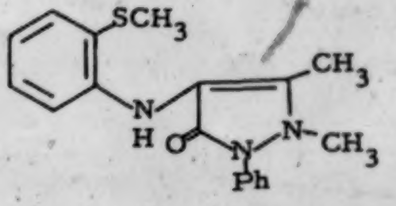
Scheme 23

spiro-benzothiazoline (403) which then further reduced to the 4-(2-mercaptophenylamino)pyrazolone (406). It is believed that this intramolecular condensation could also occur under neutral conditions because the same products were isolated when the nitro compound (400a) was reduced by zinc and ammonium chloride in aqueous ethanol.

In order to verify the assumption that the spiro-benzothiazoline(403) is obtained first then further reduced to compound (406), a pure sample of (403) was reduced by sodium borohydride and palladium-charcoal in a mixture of dioxane and dilute sodium hydroxide solution. As expected, compound (406) was the main product isolated.

Methylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-pyrazolin-5-one (406):

Initially, attempts to methylate this compound with diazomethane only resulted in its oxidation to the spiro-benzothiazoline (403). However, when (406) was dissolved in cold dilute sodium hydroxide solution and dimethyl sulfate was added dropwise, an insoluble product separated. Crystallization of this product yielded a compound which analyzed correctly for $C_{18}H_{19}N_3OS$. An accurate mass measurement of the molecular ion at m/e 325 verified this formula. This compound was identified as the dimethyl derivative 2,3-dimethyl-4-(2-methylthiophenylamino)-1-phenyl-3-pyrazolin-5-one (408).



(408)

Methylation at N-2 of the pyrazolone nucleus was indicated by the i.r. spectrum which displayed a C=O absorption band at 1670 cm^{-1}. Such a band is only expected when the pyrazolone ring exists in the "NH" form (408) (Nakanishi, 1962; Newman and Pauwels, 1969). The mass spectrum of this dimethyl derivative (Fig. 11, Scheme 24) had a strong ion (the base peak) at m/e 56. This ion, which corresponds to $CH_3-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow CH_3-\overset{+}{C}=N-CH_3$, was found in the spectra of antipyrine, aminopyrine (see part III A) and in the spectrum of the N-methylpyrazolone (324) prepared earlier in this study. The

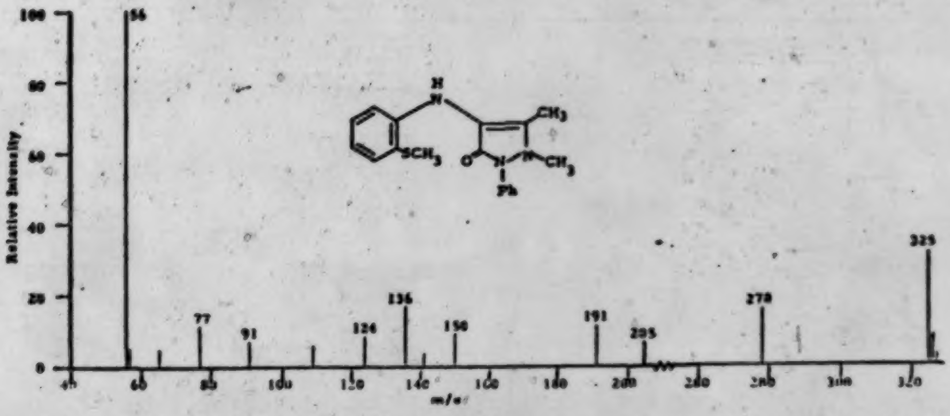
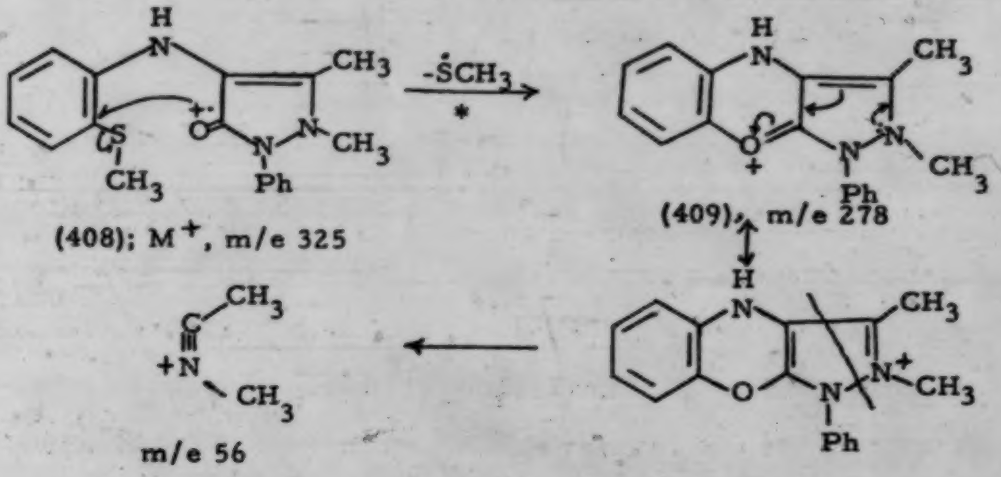


Fig. 11: A portion of the mass spectrum of 2,3-dimethyl-4-(2-methylthiophenylamino)-1-phenyl-2-pyrazolin-5-one (408).

fact that S-methylation had occurred was substantiated by the chemical properties and the mass spectrum of this compound. The product obtained was no longer soluble in sodium hydroxide solution which indicated replacement of the hydrogen of the thiol function. Also an S–H stretching band was not detected in the i.r. or in the n.m.r. spectra. The mass spectrum of this compound (Scheme 24) was most informative. It gave a molecular ion at m/e 325 ($C_{18}H_{19}N_3OS$) and an abundant $(M-47)^+$ fragment ion ($C_{17}H_{16}N_3O$). This accounted for the loss of an SCH_3 radical from the molecular ion, a fragmentation supported by the presence of a metastable ion. The loss of OCH_3 or SCH_3 radicals from ethers or thioethers is not a common fragmentation pathway, but might be expected to occur if it leads to a stable even electron cyclic ion such as (409). A similar _ortho_ effect was



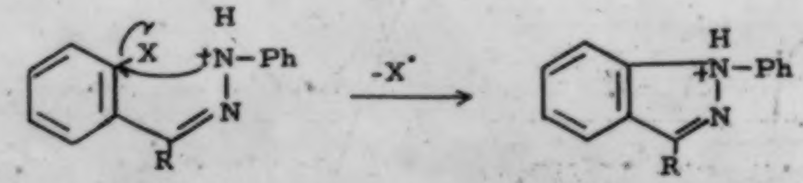
(408); M⁺, m/e 325

(409), m/e 278

m/e 56

Scheme 24

recently reported by Cable _et al_ (1972) who examined the mass spectra of phenylhydrazones and 2,4-dinitrophenylhydrazones of _ortho_ substituted benzaldehydes and acetophenones. They found that a fragment ion resulted from the loss of the ortho group (I, Br, Cl, OH and OCH_3) as a radical. This process leading to an $(M-X)^+$ ion was visualized as the internal displacement of the ortho-substituent by the charge localized on the amino nitrogen of the diphenylhydrazone (410) leading to the even electron cyclic ion (411).

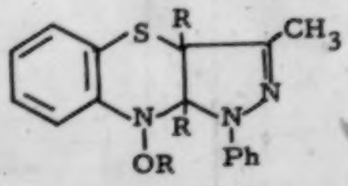


(410) (411)

The n.m.r. spectrum of the methylated product was also consistent with the proposed structure (408). It displayed three 3-proton singlets at δ2.14, 2.39 and 3.03, which are assigned to the C-CH_3, S-CH_3 and N-CH_3 groups respectively since the equivalent C-CH_3 group in the non-methylated compound (406) was detected at δ2.04 and the equivalent N-CH_3 group in antipyrene (329) came to resonance at δ2.94. The n.m.r. spectrum also contained a deuterium-exchangeable proton at δ6.12 which was assigned to the N-H proton.

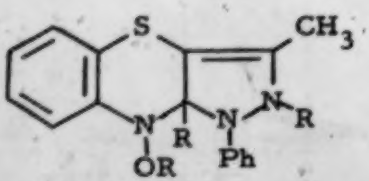
Benzoylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-pyrazolin-5-one (406):

Benzoylation of compound (406) was carried out in the manner described by Pound (1970). Treating a sodium hydroxide solution of (406) with benzoyl chloride resulted in a semisolid which, when chromatographed on a silica gel column, produced several dark oils. One of these oils solidified on repeated trituration with petroleum ether. The elemental analysis ($C_{37}H_{27}N_3O_4S$) and the mass spectrum ($M^{+\cdot}$, m/e 609) of this compound revealed that it was a tribenzoate derivative. An accurate mass measurement of the molecular ion was in agreement with this molecular formula. Two structures (412) and (413) were suggested earlier (Pound, 1970) for this compound but these suggestions were based on identification of the non-benzoylated derivative as the N-hydroxybenzothiazine (402). However, after reassessment of this structure, the tribenzoyl derivative is now identified as: 4-[N-benzoyl-N-(2-benzoylthiophenyl)amino]-5-benzoyloxy-3-methyl-1-phenylpyrazole (414). That O-benzoylation had occurred was shown from the i.r. spectrum which displayed a C=O absorption band at 1758 cm^{-1} (cf. p. 90) and by examining the mass spectrum of the product which showed the expulsion of a benzoyloxy radical (PhCOO•) from the molecular ion. A strong metastable at m/e 391.04 indicated that this expulsion was, at least in part, directly from the molecular ion. Benzoylation of both the NH and SH functions was apparent from the absence of any NH or SH absorption bands in the i.r. spectrum. In addition, a C=O absorption band at 1679 could be attributed to both S-benzoyl and N-benzoyl functions. The latter is known to absorb in this region. Also diarylthiol esters are reported to absorb close to 1685 cm^{-1} (Nyquist and Potts, 1959; Baker and Harris, 1960; Bellamy, 1968).

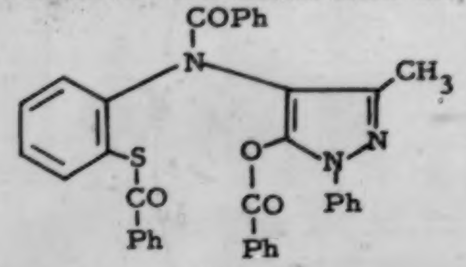


(412)

R=COPh



(413)



(414)

The mass spectrum of compound (414) is shown in Fig. 12 and the proposed fragmentation pathway are presented in Scheme 25.

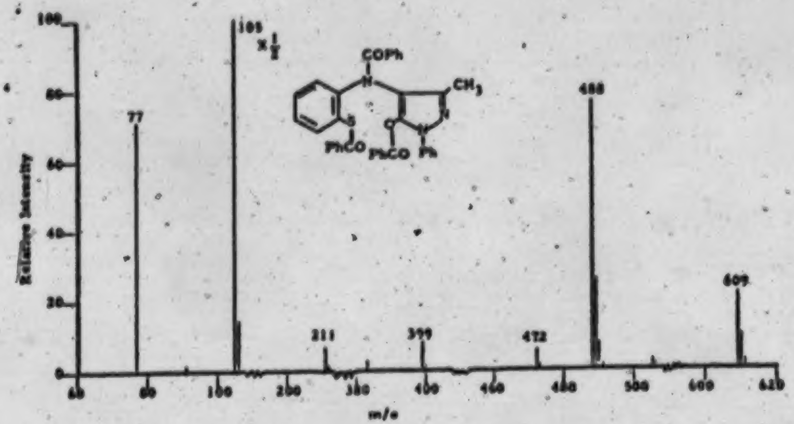
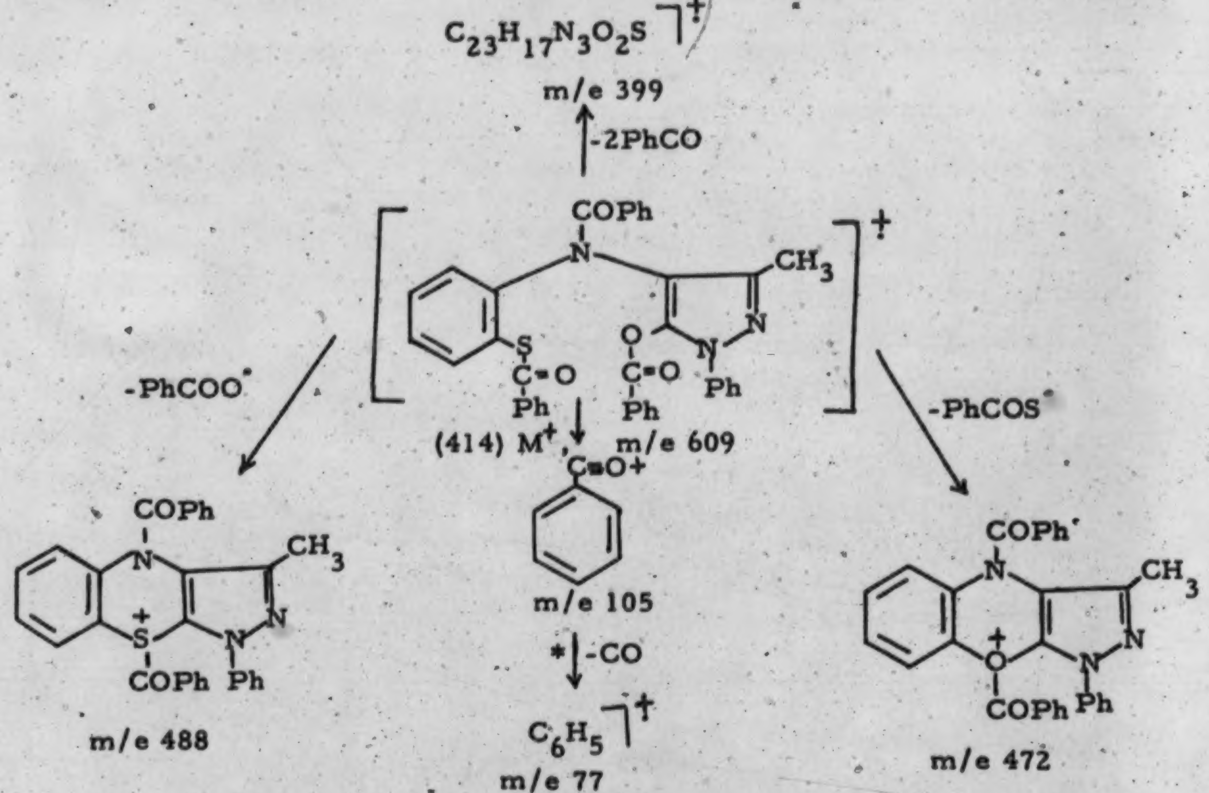


Fig. 12: A portion of the mass spectrum of 4-[(N-benzoyl-N-(benzoylthiophenyl)amino]-5-benzoyloxy-3-methyl-1-phenylpyrazole (414).

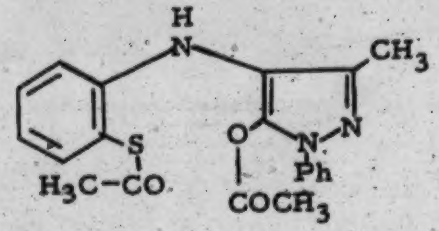

$C_{23}H_{17}N_3O_2S$]+
m/e 399
-2PhCO
COPh
N
CH3
N
N
S
C=O
Ph
O
C=O
Ph
Ph
(414) M+, m/e 609
-PhCOO•
-PhCOS•
C=O+
m/e 105
*-CO
C_6H_5]+
m/e 77
COPh
N
CH3
S+
N
N
COPh
Ph
m/e 488
COPh•
N
CH3
O+
N
N
COPh
Ph
m/e 472

Scheme 25

In addition to the major loss of PhCOO$^{\bullet}$ radical from the molecular ions, two weak fragment ions at m/e 472 and m/e 399 correspond to the expulsion of a PhCOS$^{\bullet}$ and two PhCO$^{\bullet}$ radicals from the molecular ion. Although no metastables to support these two losses are present, the absence of other ions in the spectrum suggested that they originate directly from the molecular ion. As usual in all the benzoyl derivatives, the spectrum showed a strong ion at m/e 105 (PhCO)$^+$ which expelled a carbon monoxide molecule to give another strong ion at m/e 77 (C_6H_5).

Acetylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-pyrazolin-5-one (406)

Trials to acetylate compound (406) by heating with acetic anhydride or acetyl chloride in benzene were unsuccessful and resulted only in the isolation of the spiro-benzothiazoline (403). However, when compound (406) was treated with acetic ahydride in cold pyridine, a yellow NaOH-insoluble product was collected. Crystallization of this compound proved difficult but the i.r., the n.m.r. as well as the mass spectra indicated that it was a diacetate which is identified as 5-acetyloxy-3-methyl-4-(2-acetylthiophenylamino)-1-phenyl-pyrazole (415).



(415)

The i.r. spectrum of this compound had an N—H absorption at 3368 cm^{-1} and two C=O absorption bands at 1720 ($SCOCH_3$) and

1788 ($OCOCH_3$) cm^{-1}. Alkyl and aryl thioesters of the type C_6H_5 SCOR are known to absorb near 1710 cm^{-1} (Bellamy, 1968). The presence of the thioester C=O absorption in compound (415) at a slightly higher frequency than reported may be due to the presence of a bulky substituent in the o-position (cf. Schubert and Sweeney, 1955).

The n.m.r. spectrum of (415) contained three methyl signals at δ2.15, 2.22 and 2.44 and one D-exchangeable proton at δ6.2 (N–H). A molecular ion at m/e 381 in the mass spectrum of the product is in agreement with the diacetate structure. This ion fragmented by two successive losses of ketene molecules. Also, a loss of a molecule of acetic acid from both the molecular ion and the $(M-42)^+$ ion was demonstrated by the fragment ions at m/e 321 and 279.

Attempts to isolate the diacetyl derivative (415) in a pure crystalline form gave only, after long standing in ethanol, a crystalline compound which was shown to be the spiro-benzothiazoline (403). This compound is believed to be formed from the diacetyl derivative (415) by hydrolysis then oxidation since none of the spiro-benzothiazoline (403) was demonstrated in the i.r. or the n.m.r. spectra of the crude acetylation product.

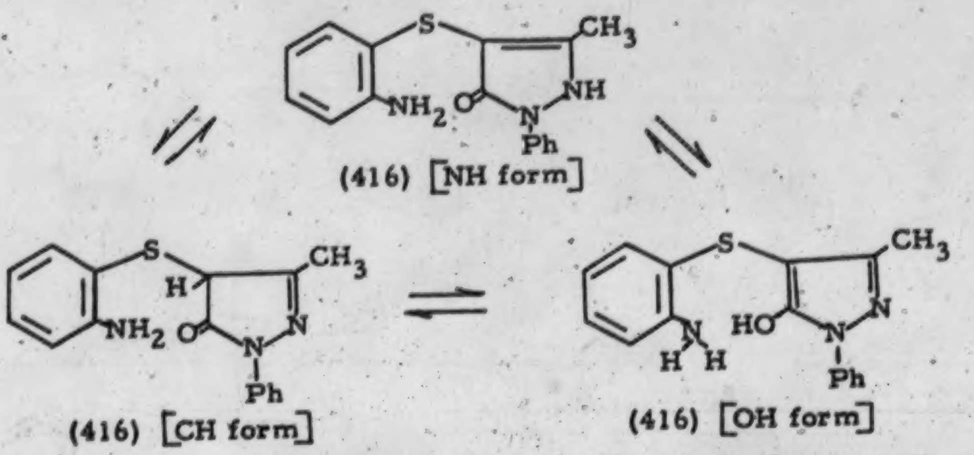
Method (B): Use of sodium borohydride and palladium-charcoal in dioxane.

It was shown earlier in this study that changing the solvent system in the sodium borohydride/palladium-charcoal reductions of the o-nitrobenzylidene derivatives (318) from sodium hydroxide solution to dioxane resulted in the formation of cyclic N-hydroxy.

compounds as major products. To find out whether it was possible to obtain any related N-hydroxy compounds from the o-nitrophenylthio derivative (400a), the sodium borohydride/palladium-charcoal reduction was carried out in dioxane. However, even when several modifications in the reduction time and/or the quantities of reducing agents were made, only two products, the thiol (406) and the spiro-benzothiazoline (403) were obtained, but this time the latter (403) was the major product. The amine (416) was not isolated in any appreciable amount from the reduction mixture; this amine was claimed earlier (Pound, 1970) to have been the major product obtained when the sodium borohydride/palladium-charcoal reduction of (400a) was carried out in dioxane.

Method (C): Use of iron and ferrous ammonium sulfate.

Reduction by means of iron and ferrous ammonium sulfate is a common method for the reduction of nitro compounds to the corresponding amines (Hickenbottom, 1959). However, when this reduction was performed earlier in this thesis with the o-nitrobenzyl derivative (319a), the cyclic N-hydroxy compound (338) was isolated along with the amine (321). When the o-nitrophenylthio compound (400) was reduced in a similar way, no cyclic N-hydroxy compounds were obtained; only the amine (416) was isolated in a good yield. Identification of this amine was based on comparison of its physical and chemical properties with those reported earlier (Angelini and Martani, 1955; Pound, 1970). The i.r. spectrum of this amine (416) indicated that it is present in the solid state in the NH $\rightleftharpoons$ OH forms. As observed with the related amines (321), the C=O and the primary amines absorption bands of compound (416) were located at lower frequencies than expected (1625, 3145 and 3295 cm^{-1}). This shift


(416) [NH form]

(416) [CH form]

(416) [OH form]

may be accounted for by the possibility of intermolecular or even intramolecular hydrogen bonding.

The mass spectrum of compound (416) was recorded (Fig. 13) and its major fragmentation pathways are suggested in Scheme 26.

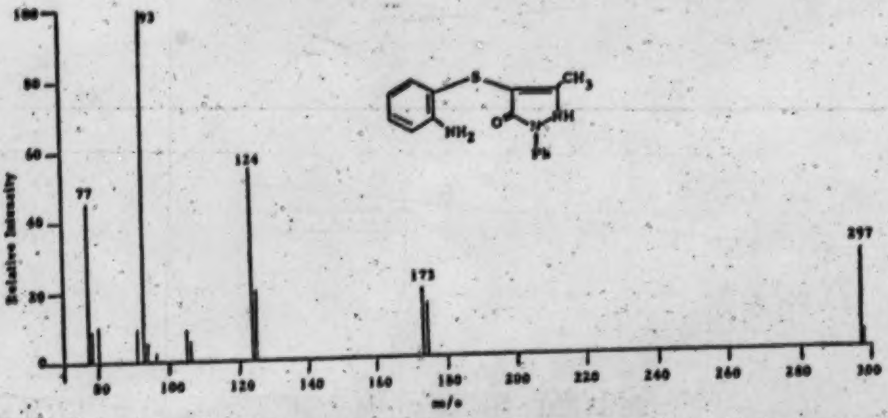
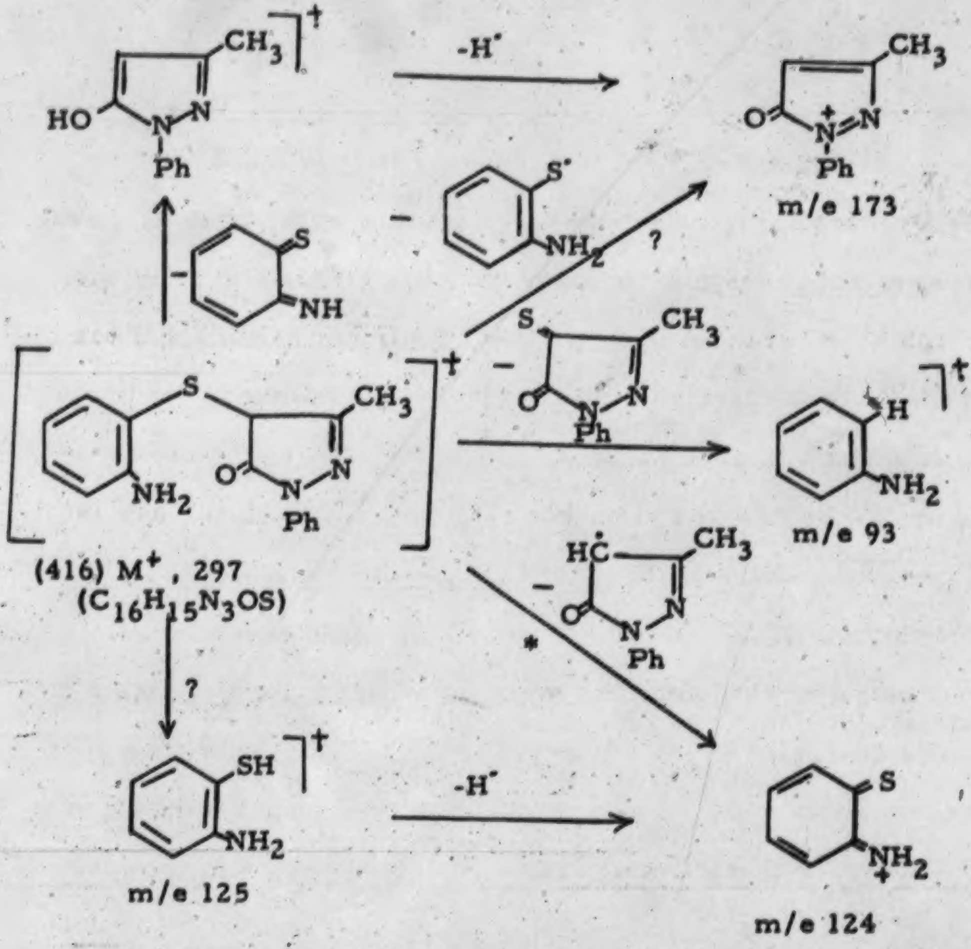


Fig. 13: A portion of the mass spectrum of 4-(2-aminophenylthio)-3-methyl-1-phenyl-3-pyrazolin-5-one (416).

Cleavage of the C—S bond occurred on both sides of the sulfur atom. Some differences exist in the behavior, under electron impact, of this amine (416) and the related amines (321) discussed earlier (p. 83). These included the absence here of both the (M-18)$^+$ and (M-19)$^+$ ions. This spectrum also had an ion at m/e 105 (PhN$_2$)$^+$ which was absent from the spectrum of (321).



Scheme 26

Method (D): Use of Zinc and ammonium chloride.

This method is commonly used to prepare hydroxylamine derivatives from nitro-compounds. Reduction of (400a) was carried out under nitrogen using aqueous ethanol as a solvent due to the insolubility of the nitro compound (400a) in water alone. This resulted in an excellent yield of the spiro-benzothiazoline (403). When the reduction period was prolonged, the thiol (406) was the main product. Replacing aqueous ethanol by aqueous tetrahydrofuran as a solvent system also resulted in isolation of the same products. In no case, was it possible to isolate any hydroxylamine or cyclic N-hydroxy compounds.

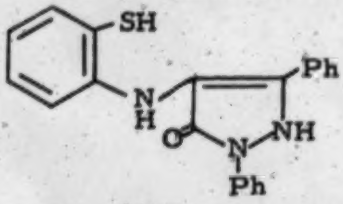
Method (E): Catalytic Hydrogenation.

Finally, the nitro compound (400a) was reduced catalytically over platinum. Formation of cyclic N-hydroxy compounds was not likely using this strong reducing system; however, it was of interest to see if a similar reaction to that which occurred earlier during the catalytic hydrogenation of the nitrobenzyl derivatives (319a,b) would take place. This did not occur. Instead, a small amount of the thiol (406) was precipitated during the reduction and was separated from the platinum catalyst by its solubility in dilute alkali solution. The filtrate, after evaporation, yielded the spiro-benzothiazoline (403) as the major product. When the same reduction was repeated under pressure a third product identified as the amine (416) was also isolated from the reduction mixture.

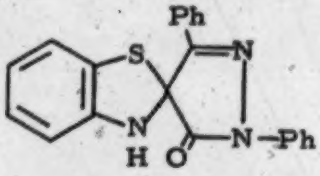
Reductions of 1,3-diphenyl-4-(2-nitrophenylthio)-2-pyrazolin-5-one (400b):

Only three of the methods used previously with the methyl analog (400a) were tried on this nitro derivative (400b). These were the sodium borohydride/palladium-charcoal reduction in 10% sodium hydroxide solution, the reduction by zinc and ammonium chloride and the reduction by iron and ferrous ammonium sulfate. The first two methods produced pure crystalline products, none of which was a cyclic N-hydroxy compound. Trials to isolate pure cyrstalline products from the reaction mixture obtained by the third method were not successful.

Reduction by sodium borohydride/palladium-charcoal was carried out in 10% sodium hydroxide solution in the same way described earlier for reduction of (400a). Two compounds were isolated from the reduction mixture and were identified as 1,3-diphenyl-4-(2-mercaptophenylamino)-3-pyrazolin-5-one (417) and spiro-[benzothiazoline-2,4'-(1',3'-diphenyl-1*H*-pyrazolin-5'-one)] (418). The latter compound is believed to be formed by the oxidation of the thiol (417) during crystallization since the i.r. spectrum of the crude product was devoid of any C=O absorption near 1700 cm^{-1}.



(417)



(418)

Compound (417) was earlier identified by Pound (1970) as the isomeric N-hydroxybenzothiazine (402, Ph instead of CH_3). However, the similarities in physical and chemical properties of this compound and the thiol (406) led to the conclusion that the proposed structure (417) is more likely. This compound which was soluble in dilute alkali solutions analyzed correctly for $C_{21}H_{17}N_3OS$. Its i.r. spectrum and mass spectrum (Fig. 14) ($M^{+\cdot}$, m/e 359) were similar to those of the methyl analog (406) and consistent with the proposed structure (417). The molecular ion fragmented mainly by the loss of a hydrogen molecule yielding the spiro-benzothazoline (418). Two minor but diagnostic fragment ions were also present and were due to the expulsion, from the molecular ion, of a molecule of water and an SH radical to give ions at m/e 341 and m/e 326 respectively. These ions are believed to be analogous to those proposed earlier for the

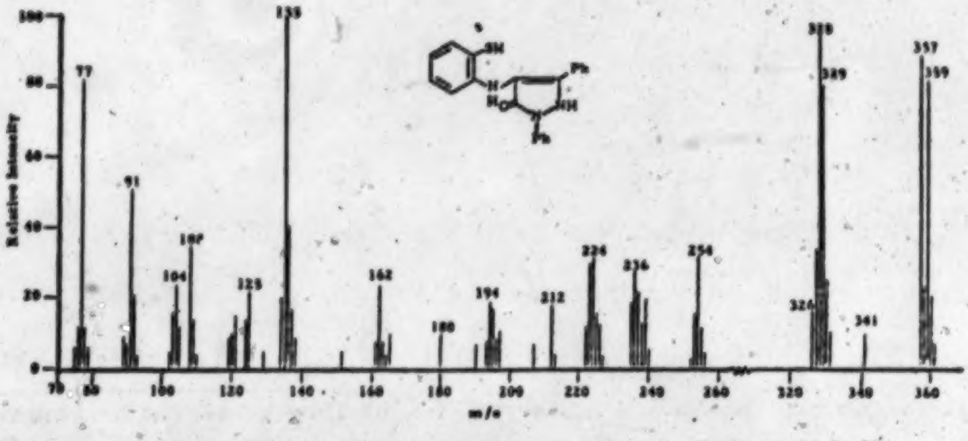


Fig. 14: A portion of the mass spectrum of 1,3-diphenyl-4-(2-mercaptophenylamino)-3-pyrazolin-5-one (417).

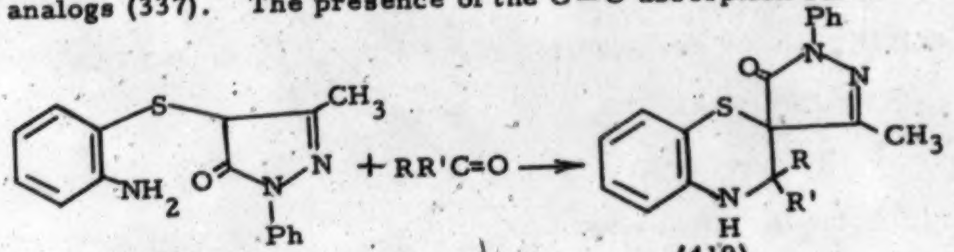
methyl analog (406) (Scheme 22, p. 171).

The spiro-benzothiazoline (418) was obtained only in minor quantities during crystallization of the thiol (417), but it was isolated in a good yield when (417) was treated with cold acetic acid. Its identification was based on its correct elemental analysis and its spectral characteristics (i.r., n.m.r. and mass spectrometry), all of which were similar to those observed for the methyl analog (403); the mass spectra of (403) and (418) are discussed later in the mass spectrometry section (part III A).

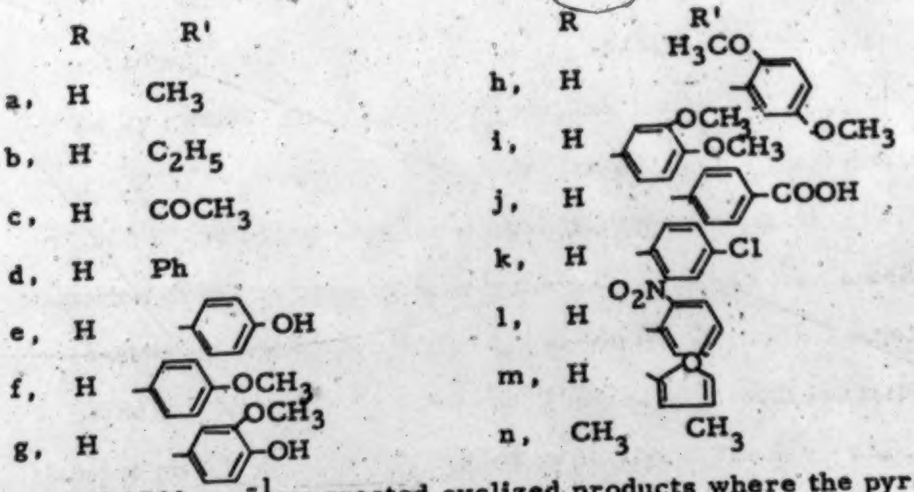
When reduction of (400b) was performed using zinc and ammonium chloride in aqueous ethanol, the spiro-benzothiazoline (418) was obtained in a good yield. Prolonging the reduction time gave a crude product devoid of the C=O absorption at 1712 cm^{-1} which was believed to be the thiol (417). However, crystallization of this crude product yielded only the spiro compound (418).

Preparation of some spiro(dihydrobenzothiazine)pyrazolones:

When 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) was reacted in refluxing ethanol with different aldehydes and ketones, the expected spiro-dihydrobenzothiazines (419) were isolated in most cases. Identification of these products as spiro-[(3-substituted-3,4-dihydro-2H-1,4-benzothiazine)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5-ones)] (419) was based on their correct elemental analysis as well as their physical and chemical properties. The i.r. spectra displayed N–H stretching and lactam C=O absorption bands similar to those observed with the spiro-tetrahydroquinoline analogs (337). The presence of the C=O absorption bands around 1700 cm^{-1} suggested cyclized products where the pyrazolone ring can only exist in the "CH" form. This cyclization was confirmed by the lack of solubility of these products (except those possessing acidic substituents) in dilute alkali solutions. In fact, some of these


S
CH3
NH2
O
N
N
Ph
+ RR'C=O
Ph
O
N
N
S
CH3
R
R'
N
H

(416)   (419)


R
R'
a, H CH3
b, H C2H5
c, H COCH3
d, H Ph
e, H OH
f, H OCH3
g, H OCH3 OH
R
R'
h, H H3CO OCH3
i, H OCH3 OCH3
j, H COOH
k, H Cl
l, H O2N
m, H
n, CH3 CH3

compounds form hydrochloride salts, though with difficulty. The n.m.r. spectra of these derivatives also supported the assigned structures. In addition to the pyrazolone C-3 methyl signal, and signals ascribable to the aromatic protons and the different substituents at C-3 of the dihydrobenzothiazine ring, each spectrum contained a one-proton signal near δ 4.8 ($>C\underline{H}R$) and another D-exchangeable NH signal of variable chemical shift. A common feature in most spectra was the appearance of two signals for both the pyrazolone C_3-methyl group and the CH group. The separation between these two signals was as low as 3 Hz (R=*p*-hydroxyphenyl) and as high as 14 Hz ($R=CH_2CH_3$). This separation was absent in compound (419n) where $R=R'=CH_3$ and also in compound (419c) were R=H and $R'=COCH_3$. This signal duplication is concluded to be due to the possibility of mixtures of positional isomers in which the methyl group of the pyrazolone ring is either in *cis* or *trans* position with respect to the substituent at C-3 of the dihydrobenzothiazine nucleus. However, an attempt to separate isomers of compound (419l, R=H and R'= *o*-nitrophenyl) by means of fractional crystallization failed.

The mechanism of formation of these dihydrobenzothiazines (419) is believed to be the same as that suggested earlier for the formation of the related tetrahydroquinolines. As was noted earlier, the reaction of the amine (416) with acetone required a longer time and higher reaction temperature. The reaction with formaldehyde produced an oil which was difficult to purify. The i.r. spectrum of this product showed a C=O absorption band at 1710 cm^{-1} but no NH or OH absorptions were present. This was not investigated further.

The mass spectra of some of these compounds (419) were recorded (Figs. 15 and 16) and some tentative fragmentation pathways are suggested in Scheme 30. Attempts to deuterate one of the simple derivatives failed but it proved possible to partially deuterate compound (419i). This, in addition to accurate mass measurements (Table 4) of some of the fragment ions in (419d) was helpful in accounting for the fragmentation pattern observed.

Table 4. Accurate Mass Measurement Data of some of the Important Ions in the Mass Spectrum of the Spiro-(dihydrobenzothiazine)pyrazolone (419d).

Measured m/e	Composition	Required m/e	Designation*
352.1447	$C_{23}H_{18}N_3O$	352.1449	c or c'
212.0532	$C_{13}H_{10}NS$	212.0534	d or d'
181.0889	$C_{13}H_{11}N$	181.0892	g
121.0109	C_7H_5S	121.0111	h

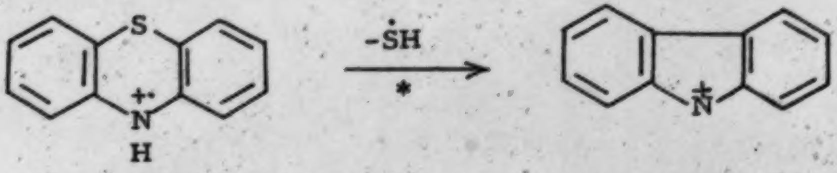
* as in Scheme 30.

Unlike the spiro-benzothiazoline derivatives (431) (part III A), most of the fragmentation pathways demonstrated here took place in the dihydrobenzothiazine nucleus rather than in the pyrazolone ring. Some similarities with the fragmentation of the spiro-tetrahydroquinoline derivatives (p. 148) were apparent although in this case more fragment ions were observed which presumably is due to the ability of the sulfur atom to localize the positive charge. With only one exception (419c, R=H and R'=$COCH_3$), these compounds displayed strong molecular ions which, in many cases, were the base peaks in the spectra. The loss of a hydrogen atom (R in all compounds except

419n) or the other substituent in the form of a radical from the C-3 position of the benzothiazine ring gave ions of relatively low abundance (ions a and b respectively). An ion analogous to a was absent from compound (419n) where R is a methyl group and also from compound (419c) where the loss of the acetyl substituent as a radical resulted in the only strong ion in the spectrum.

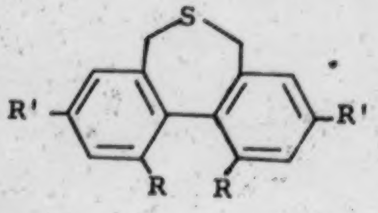
An interesting fragment ion demonstrated in all the spectra (although of very low abundance in compound 419c) was due to the direct loss of an $\dot{S}$H radical from the molecular ion. That this loss of the $\dot{S}$H radical was (at least in part) direct from the molecular ion was shown by appropriate metastables in all the spectra recorded. This, however, was not surprising since the loss of a sulfhydryl radical from cyclic sulfur compounds is a process observed by several investigators.

Gilbert and Millard (1969) found that phenothiazine (420) fragments initially by the loss of its sulfur atom either as elemental sulfur or as $\dot{S}$H or $\dot{C}$SH radicals. The origin of the hydrogen atom lost as an $\dot{S}$H radical was not clear, but they depicted it as originating from the ring nitrogen atom producing (421).

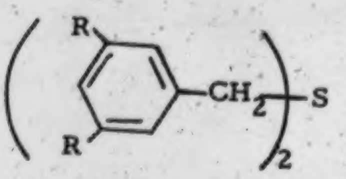


(420) (421)

Wahl (1970) also demonstrated the same loss from three bridged biphenyl derivatives (422), but he gave no explanation of the origin of the hydrogen atom(s) involved and did not suggest a formula for the resulting ion. The same investigator found that two bis-

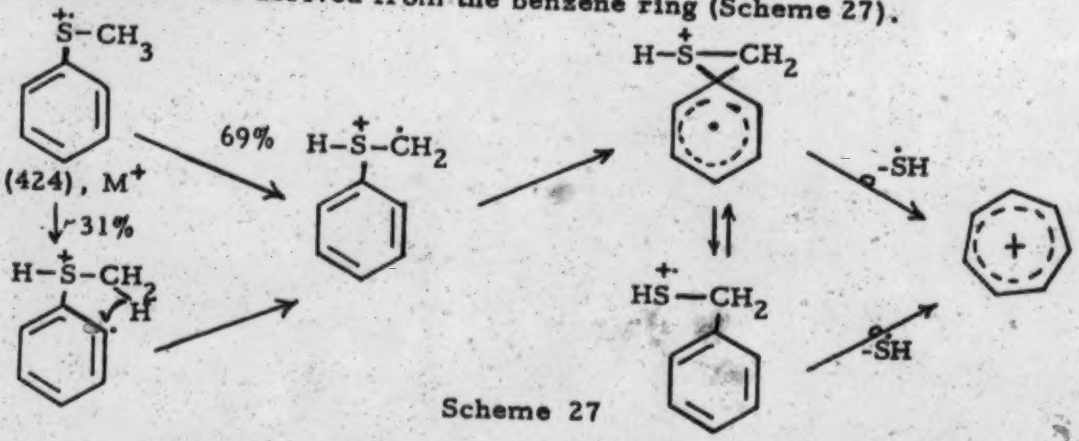


(422)



(423)

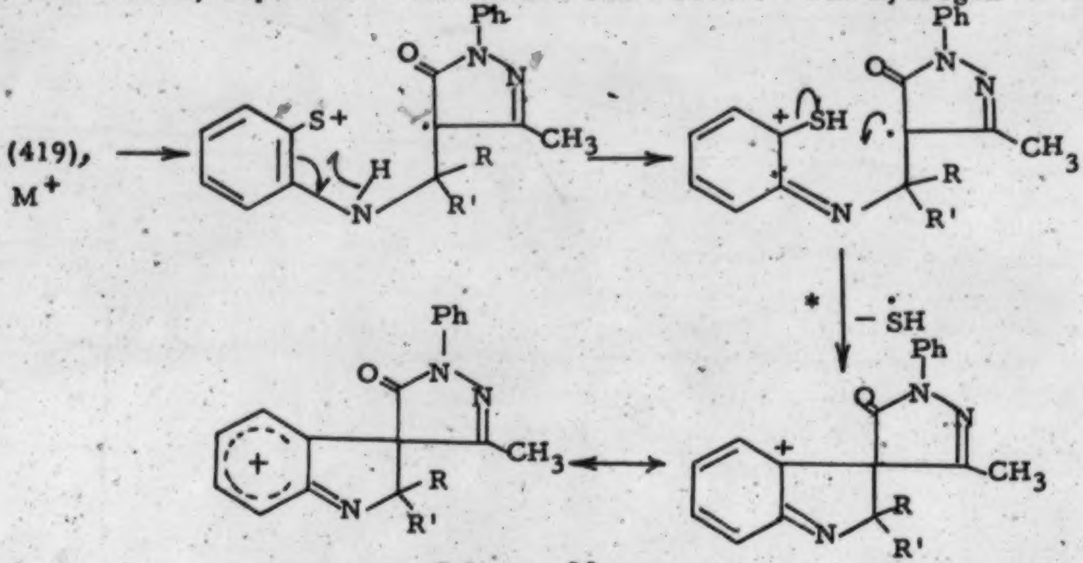
benzylic sulfides (423) closely related to the bridged biphenyl (422) showed only very minor losses of SH radicals [0.4-2% of the molecular ion compared with 55-80% in case of compounds (422)] . On the other hand, alkyl aryl sulfides such as (424) gave strong M-33 ions resulting from the expulsion of SH• radical from the molecular ion (Tatematsu et al, 1966). A study of the deuterated thioether (424, SCD_3 replaces SCH_3) indicated that one third of the hydrogen atoms of the $\dot{S}H$ radical eliminated were derived from the benzene ring (Scheme 27).



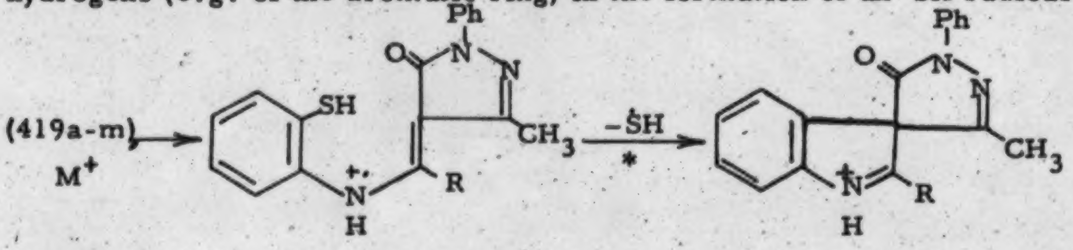
Scheme 27

In the present study, an attempt to account for the origin of the hydrogen(s) involved in the •SH loss was undertaken. Deuteration of the N-4 hydrogen atom of the benzothiazine ring in compound (419i) showed that this hydrogen is only partially involved. The molecular ion of the deuterated compound fragmented to give ions which corresponded to $(M-33)^+$ and $(M-34)^+$. The mechanism illustrated in

Scheme 28 may explain how such losses could occur. The hydrogen atom at C-3 of the benzothiazine ring may also be involved in the manner shown in Scheme 29. It may be of significance that in the spectrum of compound (419n) where C-3 is disubstituted with two methyl groups, an (M-33) ion was present in the spectrum although its relative abundance (4%) was much less than in the related compounds (e.g. 15% in 419a). No attempt was made to detect the involvement of any other hydrogens (e.g. of the aromatic ring) in the formation of an $\dot{S}H$ radical but it is believed that these may also take part in a manner similar to that shown earlier by Tatematsu et al (1966) in their studies on thioethers.



Scheme 28



Scheme 29

Another common fragment ion present in all the spectra

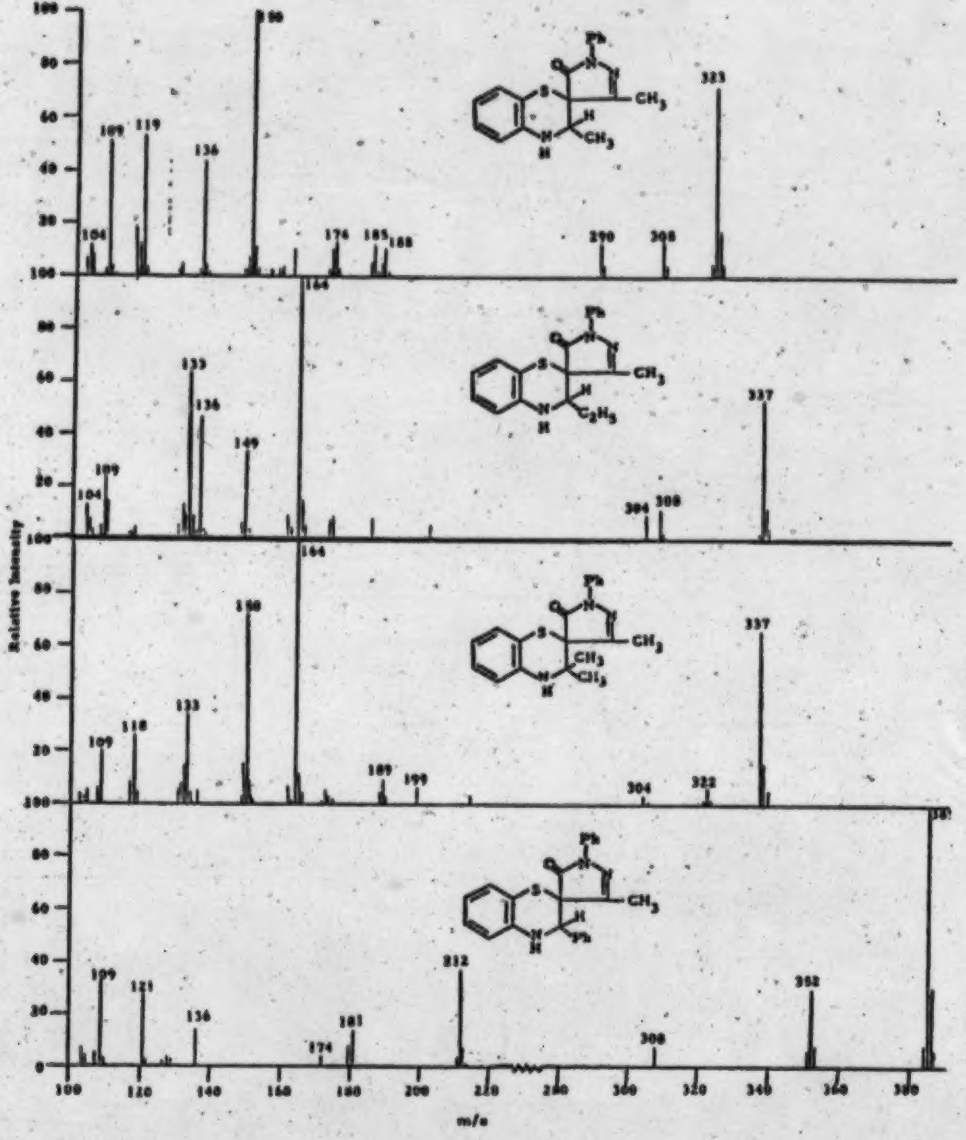


Fig. 1·5: Portions of the mass spectra of the spiro(dihydrobenzothiazine)pyrazolones (419a, b, n, d).

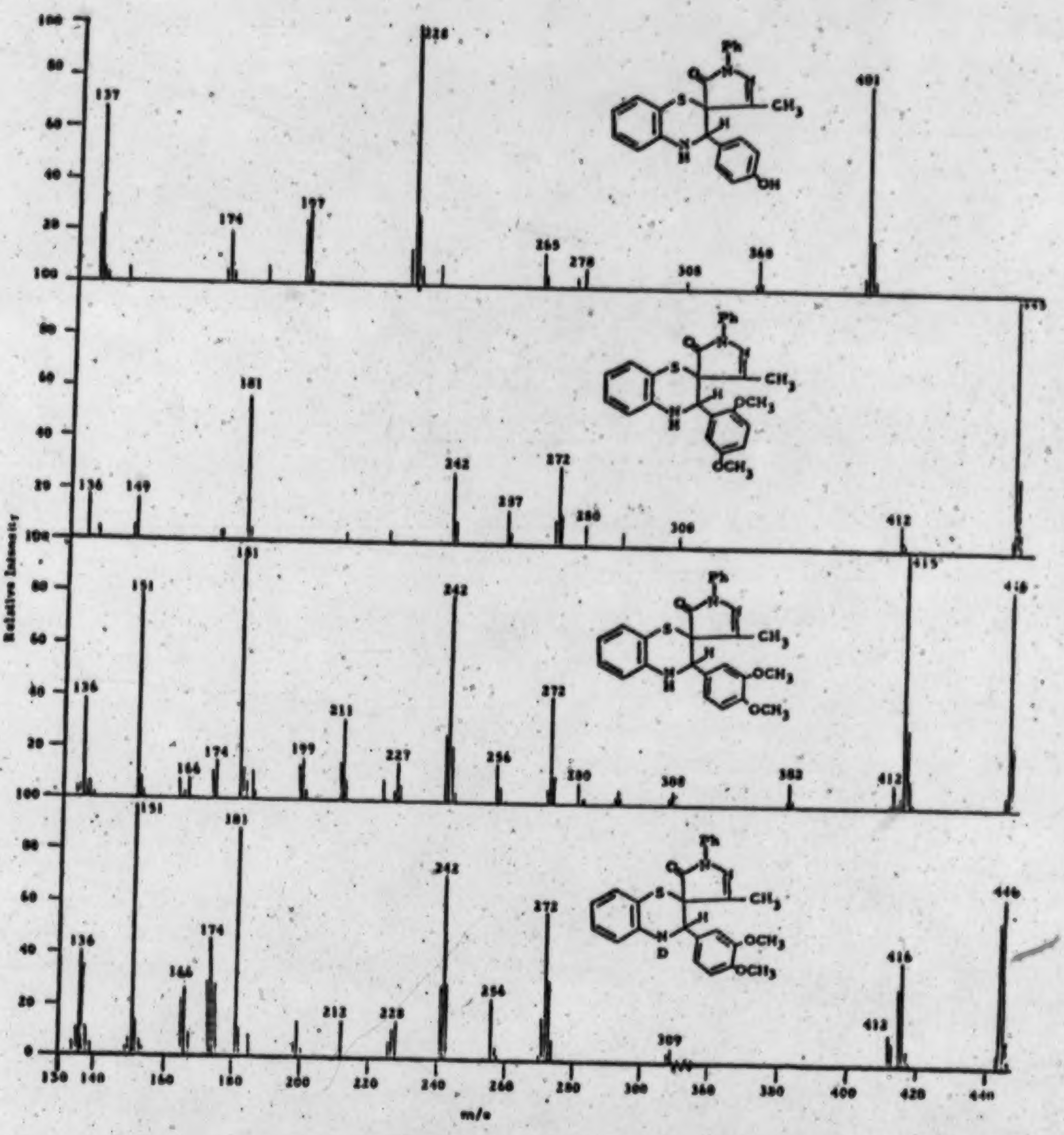
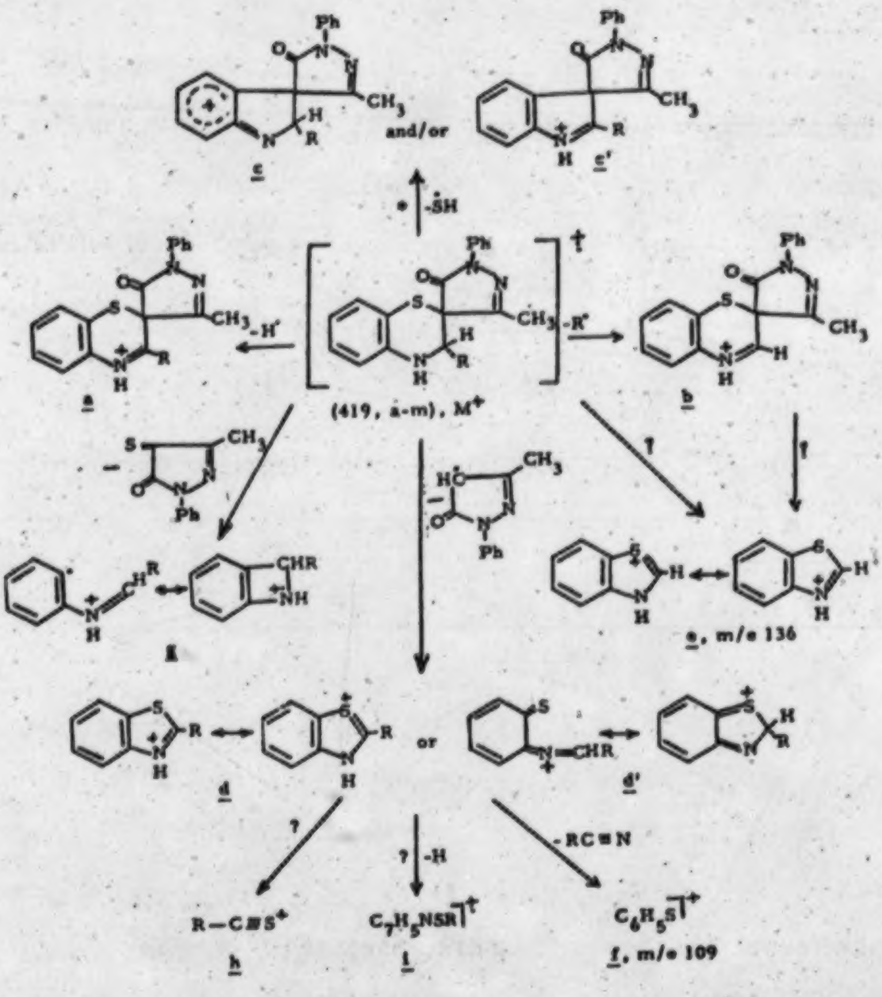
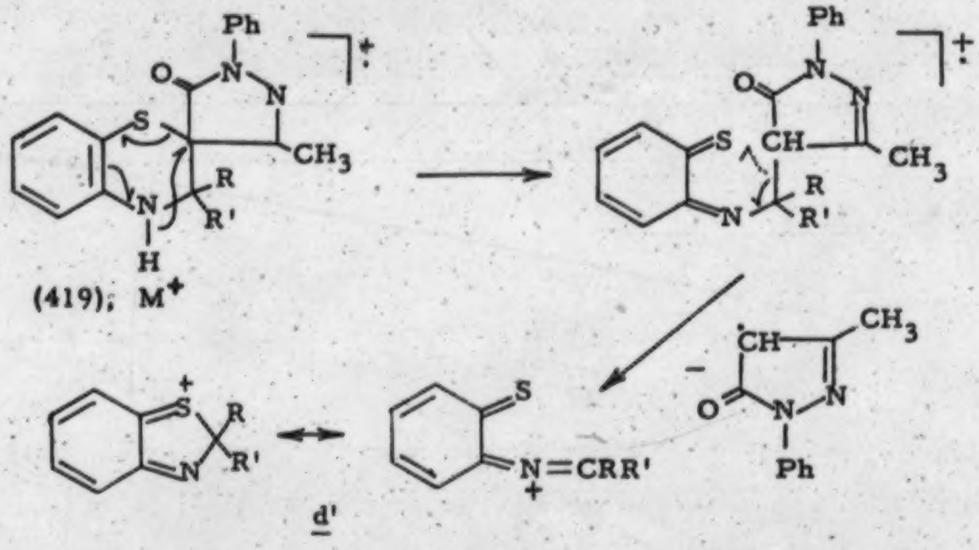


Fig. 16: Portions of the mass spectra of the spiro(dihydrobenzothiazine)-pyrazolones (419e, h, i) and the deuterated derivative of (419i).


Ph
CH$_3$
and/or
c
c'
$\cdot$SH
(419, a-m), M$^+$
-H$^\cdot$
-R$^\cdot$
a
b
Ph
?
e, m/e 136
g
d
or
d'
?
? -H
-RC≡N
R—C≡S$^+$
h
C$_7$H$_5$NSR$]^{+\cdot}$
i
C$_6$H$_5$S$]^+$
f, m/e 109

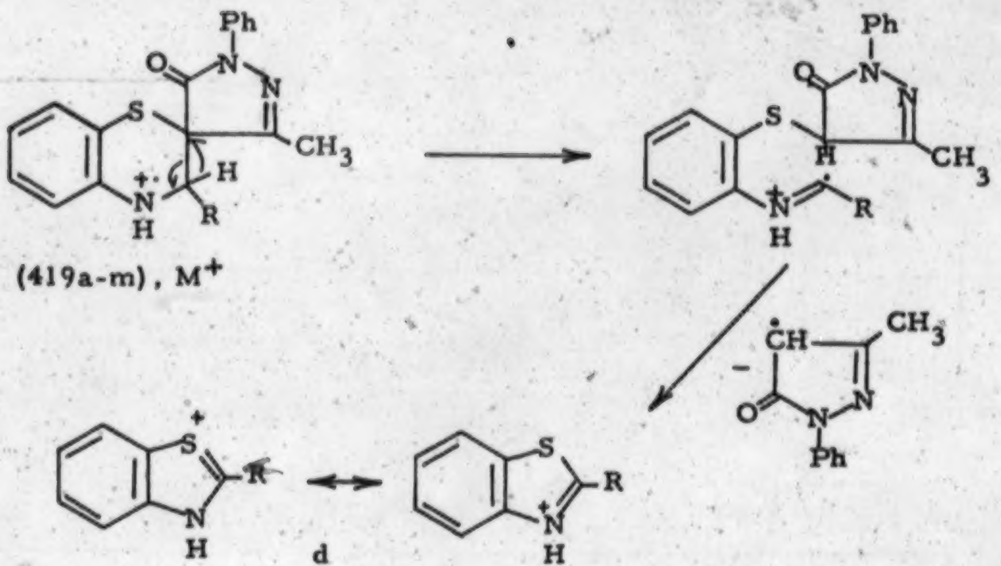
Scheme 30

was the ion postulated as d or d' which resulted from the expulsion of a pyrazolone radical from the molecular ion. A similar ion was also demonstrated in the mass spectra of the tetrahydroquinoline derivatives (337) although in the dihydrobenzothiazines (419) no metastables were found to support its direct formation from the molecular ion. Also here, deuteration of compound (419i) indicated that the hydrogen atom at N-4 of the benzothiazine ring was the one mainly involved in the loss of the pyrazolone radical (Scheme 31) since 174 mass units were lost from the molecular ion of the deuterated compound (419i, D replaces H) instead of the 173 mass units expelled from the molecular ion of (419i). Some expulsions of 173 mass units were also demonstrated in the same deuterated compound which might suggest the involvement of the hydrogen atom at C-3 (Scheme 32). However, incomplete deuteration or D→H exchange in the mass spectrometer may account for such loss.



Scheme 31

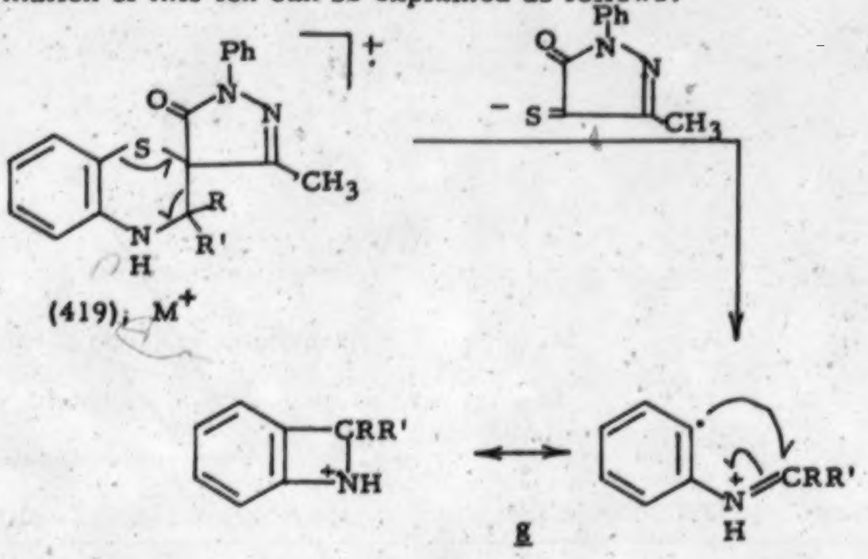
The mass spectrum of the 2,2-dimethyl compound (419n) showed a strong M-173 ion (the base peak) which adds evidence to the



Scheme 32

proposed involvement of the amine hydrogen in the formation of this ion. Another strong ion at m/e 150 in the spectrum of the same compound (419n) is formulated as ion d (R=CH_3) although the mechanism of its formation from the molecular ion is obscure. An ion at m/e 136 was found in variable intensities in all the spectra of (419a-m). This ion which is designated as e (Scheme 30) is presumably formed either from the molecular ion or from the fragment ion b. Its formation must involve complex rearrangements, and no speculation on such rearrangements is warranted.

The (M-173) ion (d or d') fragmented further by the expulsion of an $R-C\equiv N$ molecule to give the ion f, m/e 109; this expulsion was supported by the presence of appropriate metastable ions. Another major ion in all the spectra which is designated in Scheme 30 as ion g is believed to be formed directly from the molecular ion by expulsion of 204 mass units. Its identification as $RR'C_7H_5N$ was supported by an accurate mass measurement of the ion at m/e 181 in the spectrum of compound (419d) (Table 4). The formation of this ion can be explained as follows:



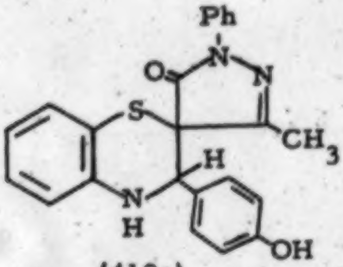
Scheme 33

An ion corresponds to the formula $R-C\equiv S^+$ as shown by accurate mass measurement of the ion at m/e 121 in compound (419d) was only demonstrated in the spectra of the derivatives in which R was an aromatic system. Apparently it is derived from ion d though no metastables were present in support of this suggestion.

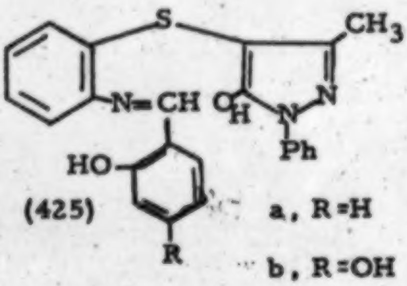
In addition to these common fragmentation pathways some other strong ions were present which resulted from the fragmentation of the substituent at C-3 of the benzothiazine ring. The $(M-COCH_3)^+$ ion in case of compound (419c) has already been mentioned. This was the only case in which the loss of the substituent at C-3 gave rise to a very strong fragment ion leaving the other fragments only minor. Compound (419i) in which R=H and R'=3,4-dimethoxyphenyl demonstrated strong frament ions at m/e 415, m/e 242 and m/e 151 which resulted from the expulsion of CH_2O molecules from the molecular ion and from ions d and h respectively. It is interesting to note that although these ions were the strongest in the spectrum of (419i), the isomeric compound (419h) in which R=H and R'=2,5-dimethoxyphenyl did not produce any ions at m/e 415 or m/e 151 and gave only an ion of medium intensity at m/e 242.

— — — —

4-(2-Aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) could be condensed with both salicylaldehyde and p-hydroxybenzaldehyde but whereas the product with the latter aldehyde was the dihydrobenzothiazine (419e), salicylaldehyde reacted with (416) to give a yellow crystalline product which is tentatively identified as the Schiff base (425a). A related product (425b) was obtained when 2,4-dihydroxybenzaldehyde was reacted with the amine (416). It appears, therefore, that the amine (416) reacts with o-hydroxybenzaldehydes in the same manner as described earlier for 4-(2-aminobenzyl)-1,3-diphenyl-5-pyrazolone (321b).



(419e)



(425) a, R=H
b, R=OH

The Schiff base structure (425) was suggested by the elemental analyses of both products ($C_{23}H_{19}N_3O_2S$ and $C_{23}H_{19}N_3O_3S$ for (425a) and (425b) respectively) and by the similarity of their i.r. spectra to those of compounds (385) (see p. 152). Medium intensity absorption bands were present at 1612 cm^{-1} (425a) and at 1610 cm^{-1}

(425b) and are assigned to the imine C=N group (c.f. Cloughetry et al, 1957). The n.m.r. spectra of (425a,b) also agreed with the Schiff base structure. In addition to the methyl and aromatic signals, a one proton $=\overset{|}{C}H$ signal was located near δ5.4 and D-exchangeable signals ascribable to the OH groups were observed in the spectra. The mass spectrum of (425a) (Fig. 17) was similar to the spectra of the spiro-dihydrobenzothiazines (419) although it differed in the relative intensities of the fragment ions formed. The ions at m/e 174 ($C_{10}H_{10}N_2O$) and at m/e 136 (C_7H_6NS), for which structures (426) and (427) are suggested, are the strongest in the spectrum of (425a) but only present in weak or medium abundance in the dihydrobenzothiazines (419). On the other hand, the M-33 and M-173 ions are much weaker in (425a) than in the cyclized compounds (419). No fragment ions were found in the spectrum of (425a) due to the fission at the ring-carbon, or ring-nitrogen bonds of the imine group. This contrasts with behavior

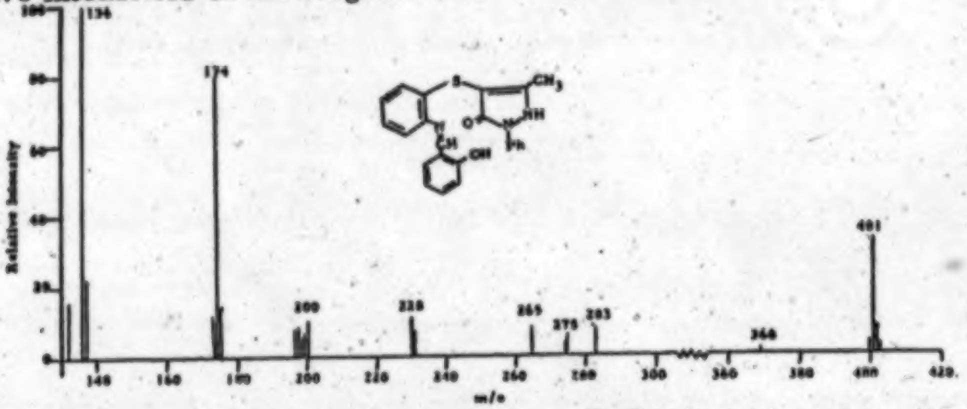
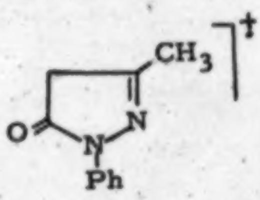
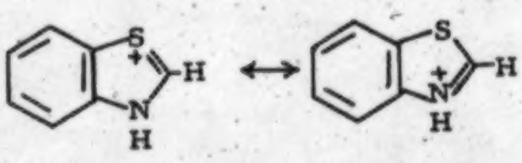


Fig. 17: A portion of the mass spectrum of 4-[2-(o-hydroxybenzylidene)aminophenylthio]-3-methyl-1-phenyl]-3-pyrazolin-5-one (425a).



(426), m/e 174

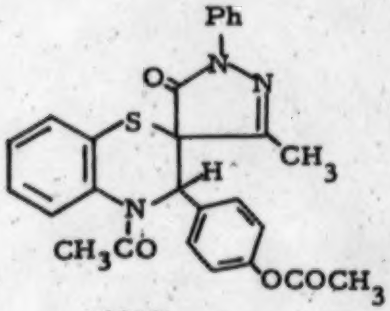


(427), m/e 136

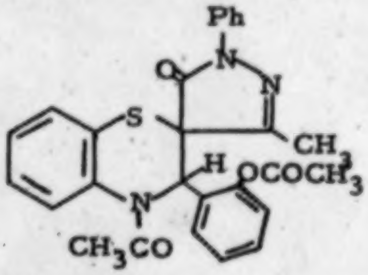
of other Schiff bases (Elias and Gillis, 1966; see p. 152 of this thesis).

The ease of solubility of compounds (425) in dilute sodium hydroxide was not very helpful in confirming the presence of an enolizable hydrogen in the pyrazolone nucleus since phenolic functions were also present. However, determination of the number of acidic hydrogens in compound (425a) indicated the presence of two phenolic and/or enolic groups in this molecule in accordance with the non-cyclized structure (425a).

Attempts to prepare a methyl derivative of (425a) by the use of dimethylsulfate or diazomethane failed. Reduction of (425a) using sodium borohydride in aqueous dioxane did not produce identifiable products. Acetylation of (425a) with acetic anhydride produced a diacetate, $C_{27}H_{23}N_3O_4S$ ($M^{+\cdot}$, m/e 485). Similarities between the i.r. spectrum of this compound and that of the diacetate (428) suggested that both compounds were structurally related. The i.r. spectrum of each displayed an ester C=O, a lactam C=O and an amide C=O in the form of a doublet. These spectra were similar to those of the diacetylated derivatives (391), (392) and (394) (see p. 156)



(428)



(429)

except that the amide C=O absorption appeared as a single band in the latter compounds. The n.m.r. spectra of (428) and diacetylated (425a) were also very similar. In both, the pyrazolone methyl signals were located far upfield (at δ 0.98 and δ 1.03) as found earlier for other acetylated dihydrobenzothiazines and tetrahydroquinolines (p.137). Based on these data, the diacetate product obtained from (425a) was assigned the cyclic structure (429). The mass spectrum of the diacetylated product (Fig. 18) supported this cyclized structure (429). It had a strong molecular ion which initially lost two ketene molecules to give an ion which fragmented further in a manner similar to that observed with the spiro-dihydrobenzothiazines (319).

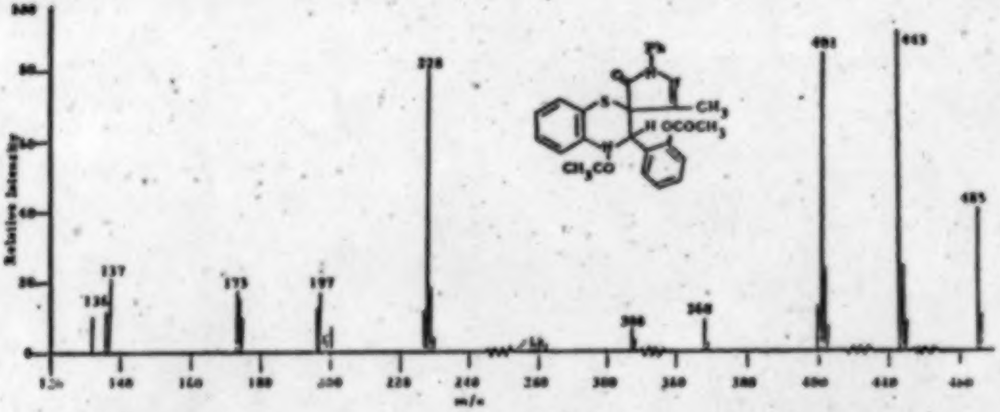
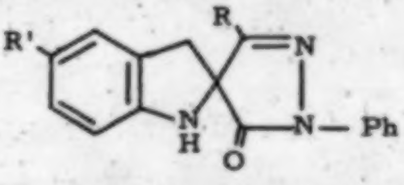


Fig. 18: A portion of the mass spectrum of spiro{[4-acetyl-3-(o-acetoxyphenyl)-3,4-dihydro-2H-1,4-benzothiazine]-2,4'-[3'-methyl-1'-phenyl-1H-pyrazolin-5'-one]} (429).

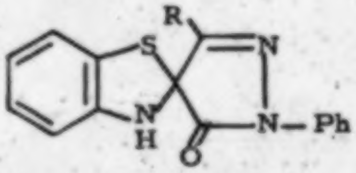
Part III: MASS SPECTROMETRY

(A) The Mass Spectra of Some Substituted Pyrazolone Derivatives

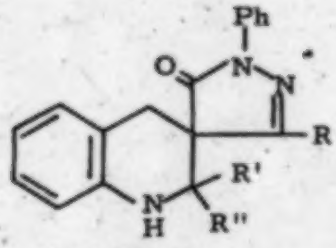
Four types of spiro-pyrazolones have been prepared and characterized in this present study. These are derivatives of spiro-[(indoline)-2,4'-(pyrazolin-5'-one)] (430), spiro[(benzothiazoline)-2,4'-(pyrazoline-5'-one)] (431), spiro[(pyrazolin-5-one)-4,3'-(tetrahydroquinoline)] (337) and spiro[(2,3-dihydro-4H-1,4-benzothiazine)-2,4'-(pyrazolin-5'-one)] (419). Many of these compounds were characterized by their mass spectra. It was noted that, in compounds (430) and (431), fission occurred mainly in the pyrazolone nucleus and produced the major fragment ions in the spectra. A literature search revealed two recent studies on the mass spectra of some simple pyrazolone drivatives (Desmarchelier and Johns, 1969b) and some substituted pyrazolone azomethine dyes (Maier *et al*, 1969) but no spiro-pyrazolones have been investigated.



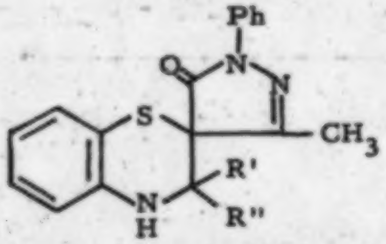
(430)



(431)

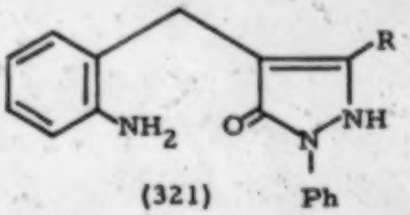


(337)

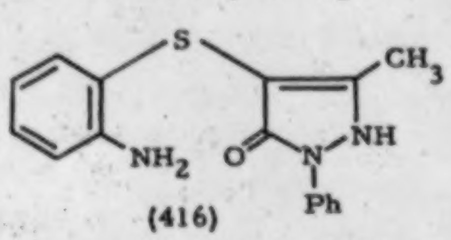


(419)

Although structurally related, the spiro(tetrahydroquinoline)pyrazoles (337) and the spiro(dihydrobenzothiazine)pyrazolones (419) fragmented differently from the spiro(indoline)pyrazolones (430) and the spiro(benzothiazoline)pyrazolones (431). The first two classes of compounds did not exhibit any major fragments which were derived from cleavage of the pyrazolone nucleus; rather fragmentation in the other part of the molecule occurred and the pyrazolone nucleus was expelled from the molecular ions as a radical. In contrast, the spectra of the 4-(2-aminobenzyl)pyrazolone derivatives (321) and their sulfur analog (416) contained relatively strong ions



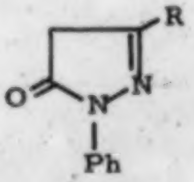
(321)



(416)

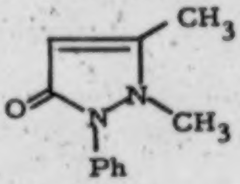
corresponding to the pyrazolone nucleus, but these ions did not fragment further to any appreciable extent. Accordingly, the spectra of these two amines (321) and (416) and the spiro-pyrazolones (337) and (419) were discussed separately earlier in this thesis. Similarities and differences between the spectra of these compounds and those now discussed in detail will be pointed out whenever there is a necessity.

In addition to the spiro-pyrazolones (430 and 431) spectra, the mass spectra of the parent pyrazolone derivatives (317), (329) and (330) were recorded and interpreted. The spectrum of one of these compounds, 3-methyl-1-phenylpyrazoline-5-one (317a), was recorded



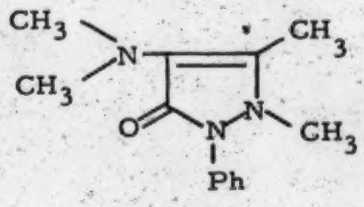
(317) a, R = CH_3

b, R = Ph



(329)

by Nishiwaki (1967) but its modes of fragmentation were not completely

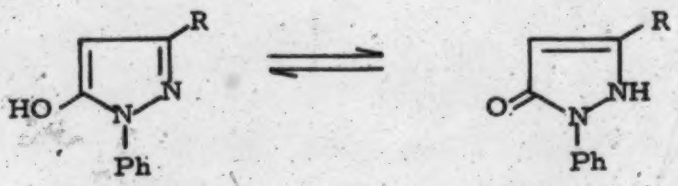


(330)

interpreted. Spectra of the two N,N-disubstituted pyrazolone derivatives, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (antipyrine) (329) and 2,3-dimethyl-4-dimethylamino-1-phenyl-3-pyrazolin-5-one (aminopyrine) (330) have been published (Tatematsu and Goto, 1965) but their fragmentation pathways were not discussed. These two compounds, in addition to their usefulness as models for the N,N-disubstituted pyrazolones, are also of medicinal interest and are present in some pharmaceutical preparations.

From the pyrazolone derivatives examined, those which are 5,5-disubstituted or which are N,N-disubstituted, have "fixed" structures and no tautomerism is possible. The others e.g. (317) can exist theoretically in one or more of the three possible tautomeric forms which were discussed earlier. For these derivatives with mobile hydrogen atoms, the tautomeric forms in the solid state were determined in order to see whether, or not, such tautomerism in the ground state would be reflected in their mass spectral behavior.

The mass spectra of the four pyrazolones (317a and 317b), (329) and (330) are shown in Figs. 19 and 20 and their suggested fragmentation patterns are illustrated in schemes 34, 36 and 37. It was shown earlier in this study that the two pyrazolones (317) exist in the solid state either in the enol "OH" form or, according to Katritzky and Maine (1964), in strongly bonded NH-form in which proton transfer (to give the OH-form) probably takes place. On the other hand, compounds (329) and (330) exist only in the NH-form.



(317-OH) (317-NH)

While the two pyrazolones (317a and 317b) displayed similar fragmentation pathways, each of the N,N-disubstituted derivatives (329) and (330) showed a unique behavior and both demonstrated some unusual modes of decomposition under electron impact. The high degree of stability of these compounds, as well as most of the other pyrazolone derivatives studied was indicated by the strong molecular ions displayed which were, in most cases, the strongest ion in the spectra.

Several initial cleavages were demonstrated in the spectra of (317a) and (317b) but only two of these gave rise to prominent fragment ions (Scheme 34). The direct expulsion of a ketene molecule ($CH_2{=}C{=}O$) from the molecular ions of both compounds gave rise to relatively strong ions (a). Also the fragment ion at m/e 105 (b) was prominent in both spectra; this ion which was attributed to the phenyl diazonium cation $(PhN_2)^+$ is believed to originate directly from the molecular ion and from the $(M\text{-}CO)^+$ ion (c) since strong supporting metastables were present at appropriate m/e values. The possibility of contribution by isobaric ions $(PhNCH_2)^+$ or $(PhCO)^+$, the latter of which could be formed by a phenyl migration, was considered but accurate mass measurement of this m/e 105 ion in the spectrum of (317a) revealed that it was solely due to $(PhN_2)^+$.

Other minor pathways in the spectra of (317a) and (317b) are the expulsion from the molecular ions of a phenyl diazonium ($PhN_2^\bullet$) and a formyl ($^\bullet CHO$) radical and a carbon monoxide (CO) molecule; the last two losses are supported by metastable ions at m/e 120.8 and m/e 122.5 in (317a) and at m/e 181.65 and m/e 183.32 in (317b)*.

The expulsion of $HN_2^\bullet$ or $RN_2^\bullet$ radicals from the molecular ion was shown to be the major initial pathway in the spectra of the pyrazolones studied by Desmarchelier and Johns (1969b). However, in compounds (317a) and (317b), this was shown to be only a minor fragmentation (3% and 1% respectively) which was followed by the expulsion of a CO molecule to produce the ion (f). This ion (f) could also arise by the loss of a $PhN_2^\bullet$ radical from the $(M\text{-}CO)^+$ ion. The strong peak at m/e 103 in compound (317b) which is attributed to a ($CH_2{=}\overset{+}{C}{-}C_6H_5$) species (ion f where $R{=}C_6H_5$) is especially strong due presumably to the stability offered by the aromatic ring in this ion.

The ion at m/e 105 (b) decomposes further by the loss of a nitrogen molecule to form the $(C_6H_5)^+$ species (i). The origin of the ion at m/e 91 which corresponds to the species $(C_6H_5N)^+$ was not

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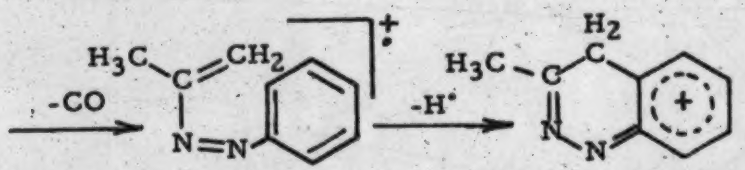
* In a recent communication published after this work was completed, Larsen et al (1973) examined the mass spectrum of (317a) and suggested a non-cyclic structure (432) for the $(M\text{-}CO)^+$ ion at m/e 146. Structure (433) was suggested for the ion at m/e 145 $(M\text{-}HCO)^+$. This suggestion was based on the finding that both the hydrogen atoms at C-4 were retained in the 4,4-d_2 analog and the ion shifted to m/e 147.

(317a), $M^{+\bullet}$



m/e 174

(432), m/e 146

(433), m/e 145

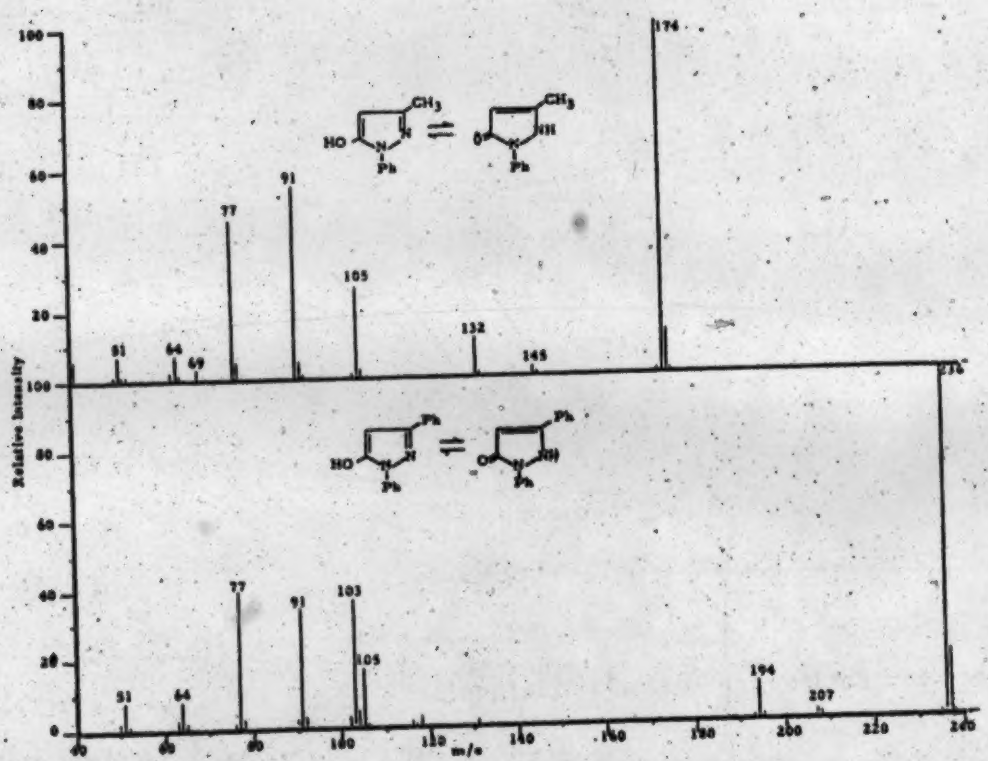
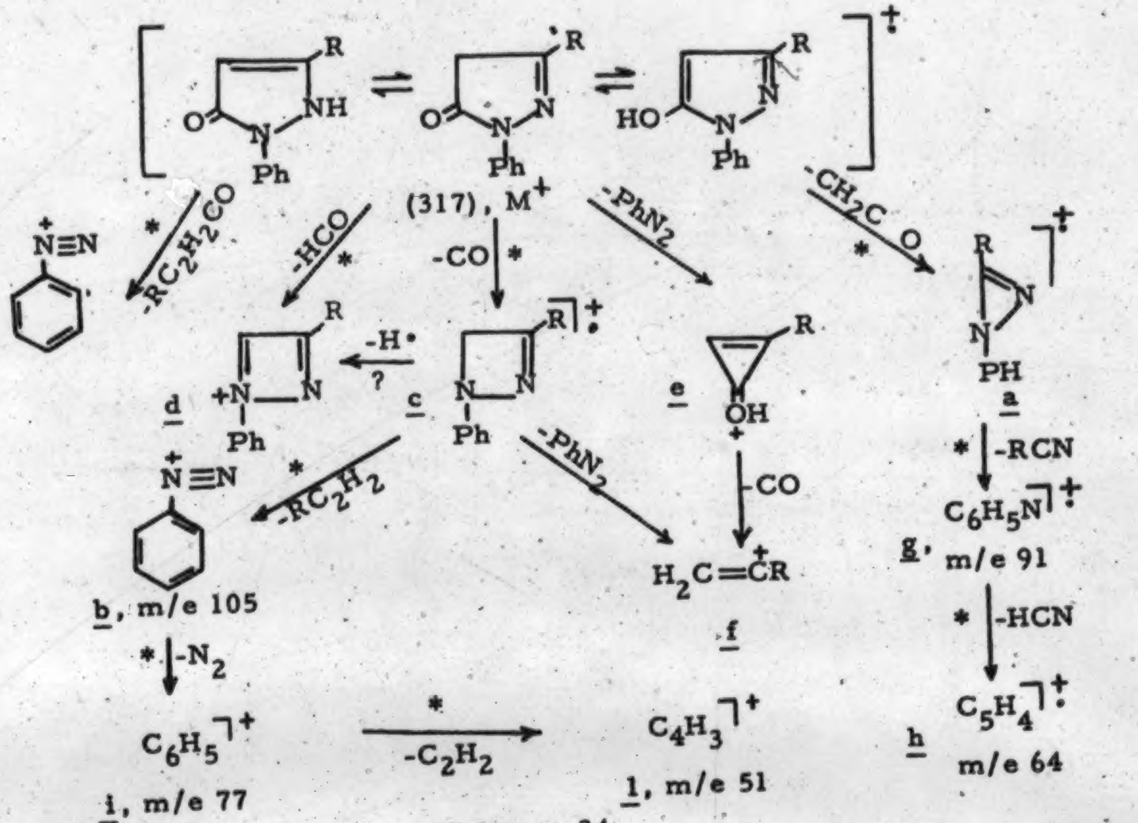


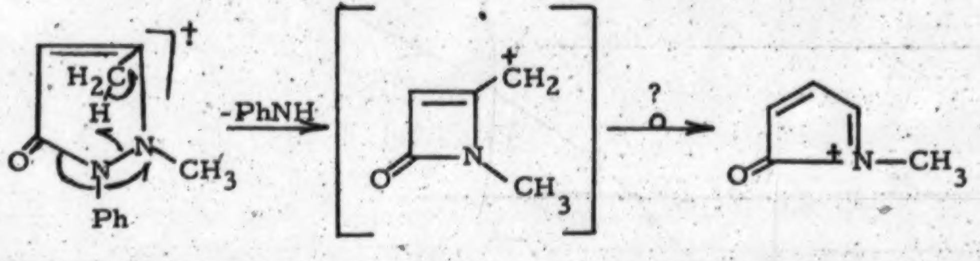
Fig. 19: Portions of the mass spectra of 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) and 1,3-diphenyl-2-pyrazolin-5-one (317b).


R
O
NH
N
Ph
HO
(317), M+
-RC2H2CO
-HCO
-CO
-PhN2
-CH2CO
-H•
?
d
c
e
a
b, m/e 105
-N2
C6H5
i, m/e 77
-C2H2
C4H3
l, m/e 51
f
H2C=CR
OH
PH
-RCN
C6H5N
g, m/e 91
-HCN
C5H4
h
m/e 64
-RC2H2
-PhN2

Scheme 34

accounted for by Nishiwaki (1967) when he studied the mass spectrum of compound (317a). The presence of metastables at m/e 62.73 and m/e 42.7 in the spectra of (317a) and (317b) respectively, suggested that this ion (g) originates from the $(M-42)^+$ ion (a) by the expulsion of either a CH_3CN or C_6H_5CN molecule. These observations indicate that an N–N bond cleavage occurs in these pyrazolones. The cleavage of such N–N bonds in compounds containing two or three linked nitrogen atoms, has been the subject of studies in many laboratories. In hydrazine (Dibeler et al, 1959), diazirine (Graham, 1962), 2,5-diphenyl-1,3,4-oxadiazole (Cotter, 1964) and indazolones (Desmarchelier and Johns, 1969a) this cleavage was found to be difficult. On the other hand, such N–N bond fission is an important fragmentation process in hydrazones (MacLeod et al, 1966), semicarbazones (Becher et al, 1966) and sulfonyl hydrazones (Bhati et al, 1966). Thuyl et al (1970) reported that the cleavage of the N–N bond and expulsion of HCN is the predominant process in the mass spectra of pyrazoles while Desmarchelier and Johns (1969b) found no evidence for initial N–N cleavage in pyrazolones. Earlier, Nishiwaki (1967), in his study of the mass spectra of pyrazoles (which included the pyrazolone (317a), reported an N–N cleavage but concluded that the initial cleavage of this bond is likely to be supressed in cases where the nitrogen is substituted. However, this was not the case with the compounds studied in the present investigation, which are all substituted at one or both nitrogens. Apart from the example already mentioned which demonstrated N–N bond cleavage and expulsion of CH_3CN or C_6H_5CN molecules from the $(M-42)^+$ ion in (317a) and (317b), evidence for initial cleavages of this linkage was found in the spectra of antipyrine (329), aminopyrine (330) and the spiro-pyrazolones (430) and (431).

The antipyrine (329) spectrum had a strong ion (84%) at m/e 96 which was second in abundance only to the base peak (the molecular ion). An accurate mass measurement of this ion revealed that it was a singlet which had the formulation C_5H_6NO. The presence of a strong metastable at m/e 49.02 suggested that it was formed directly from the molecular ion. Although clear evidence for the identity of this ion is lacking, it is represented in Scheme 36 as the ion c. This ring expanded formulation is possibly the best representation for this strong ion since it can account for the subsequent expulsion of a CH_3CN molecule to give the ion d (Scheme 36). The formation of both these major ions (c and d) as well as the strong ion at



(329), M$^+$, m/e 188

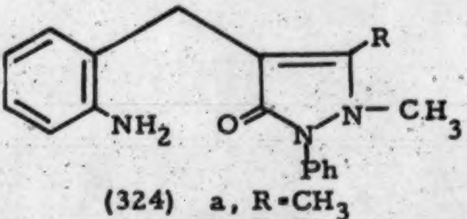
c, m/e 96

Scheme 35

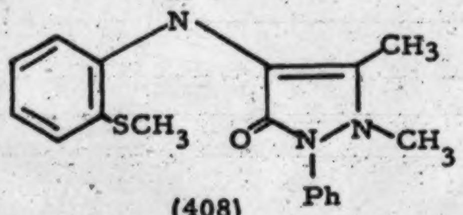
m/e 56 (ion g) indicated that N—N bond cleavage does occur as primary and secondary processes in the mass spectra of pyrazolones expecially when both nitrogens are substituted.

This same point is also illustrated in the mass spectrum of aminopyrine (329) where the base peak at m/e 56 is formed by successive losses from the molecular ion of a C_6H_5NCO molecule, a $CH_3^{\bullet}$ radical and a CH_3NC molecule (Scheme 37). All these transitions are supported by the presence of metastable ions at appropriate m/e values. The initial expulsion of a C_6H_5NCO molecule from the molecular ion again supports the possibility of initial scission of the N—N bond in the pyrazolone nucleus.

A strong ion at m/e 56 $(CH_3N{=}\overset{+}{C}CH_3 \longleftrightarrow CH_3\overset{+}{N}{\equiv}CCH_3)$ was also demonstrated in the mass spectra of the pyrazolones (324a) and (408). An equivalent ion at m/e 118 was present in the spectrum of (324b). The presence of these fragments is probably useful in the identification of 2,4-disubstituted pyrazolones.



(324) a, R=CH$_3$
b, R=Ph



(408)

Other important pathways in the spectra of antipyrine (329) and aminopyrine (330) are the expulsion of a hydrogen atom and a methyl radical from their molecular ions. The $(M-1)^+$ ions were stronger than the $(M-15)^+$ ions in both spectra. No conclusive evidence for the origin of the expelled hydrogen atom is available without labelling studies. However, there are some indications that this occurred from the N_2-methyl and not from the C_3-methyl group as was suggested by Desmarchelier and Johns (1969b). This observation is based on the finding that compound (317a), which has a C_3-methyl substituent, showed only a very weak M-1 ion (1%). The same was also noted in the spectra of all the pyrazolones studied in this investigation which had methyl substituents at the 3-position of the pyrazolone ring, while on the other hand, those N_2-methyl substituted pyrazolones such as (324) and (408) demonstrated relatively strong $(M-1)^+$ ions. This is also in accord with the spectra of the pyrazolones reported by Maier et al (1969) which showed, at most, negligible amounts of $(M-1)^+$ ions although most of them had C_3-methyl substituents.

The methyl radical losses in (329) and (330) most likely originate from N_2-methyl rather than from C_3-methyl substituents since no such loss was demonstrated in compound (317a). Also, the presence of a stronger $(M-15)^+$ ion in the spectrum of antipyrine than that in aminopyrine suggests the absence of any considerable contribution from the dimethylamino substituent in aminopyrine.

The expulsion of $PhN_2^{\bullet}$ radical from the molecular ion was demonstrated in (317a) and (317b) as only a very minor process. This loss was not observed in either antipyrine (329) or aminopyrine (330). However, an analogous loss of a $PhN{=}N{-}CH_3$ molecule was observed

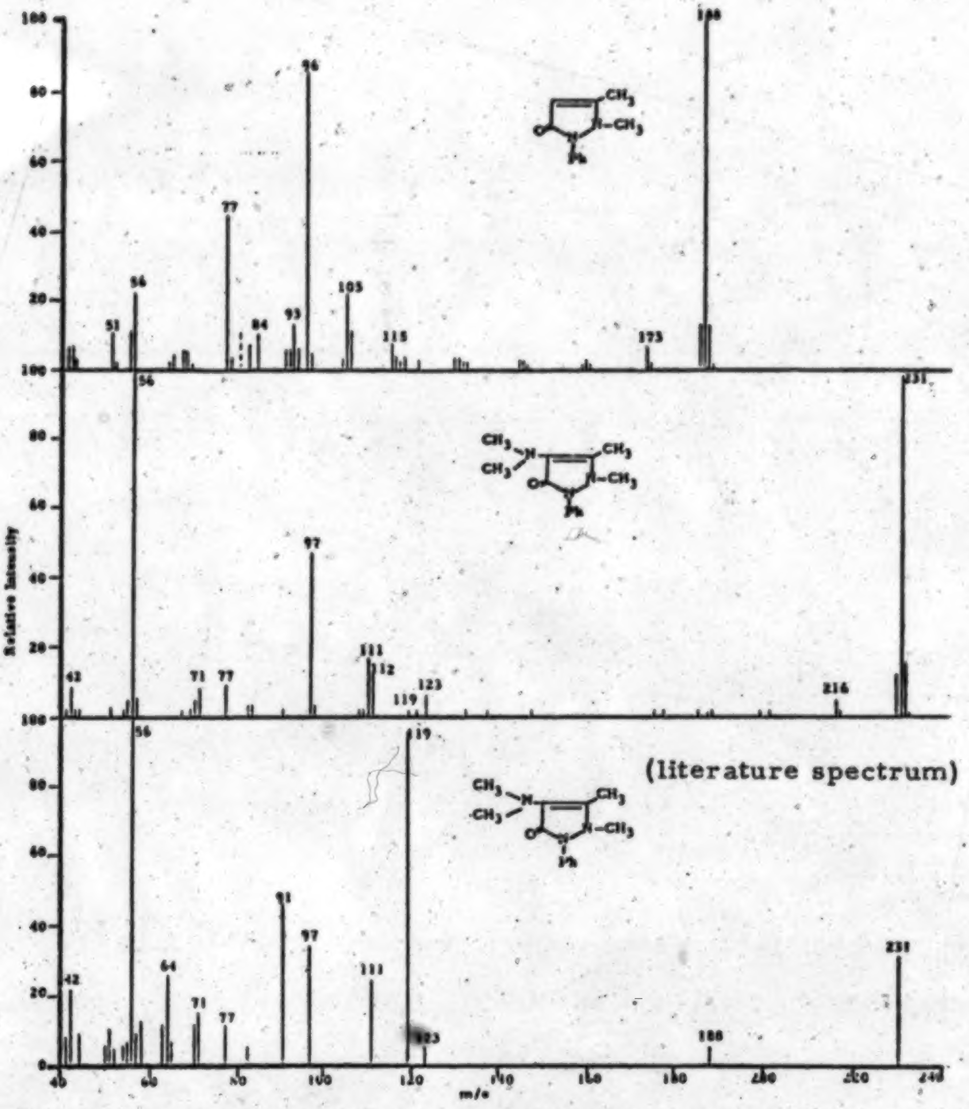
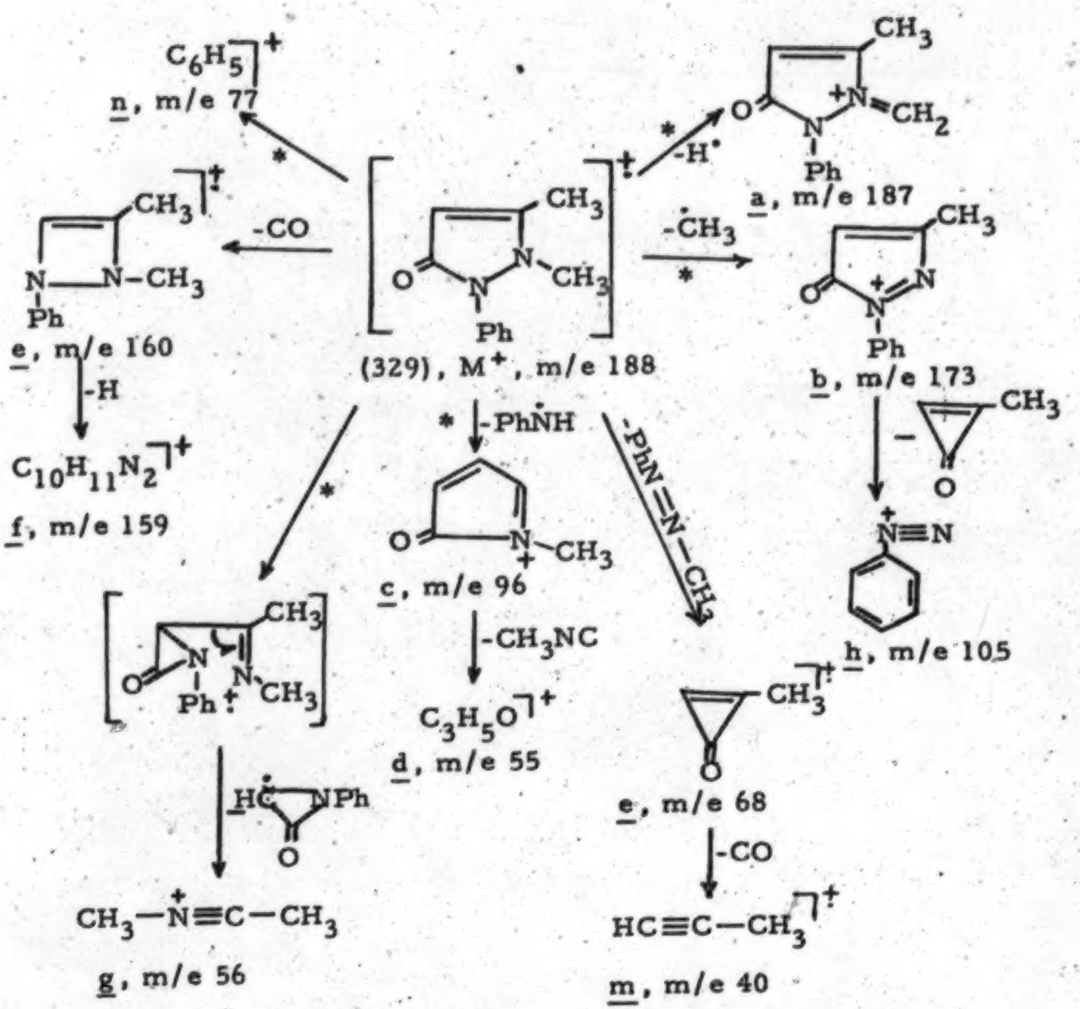


Fig. 20: Portions of the mass spectra of antipyrine (329) and aminopyrine (330).

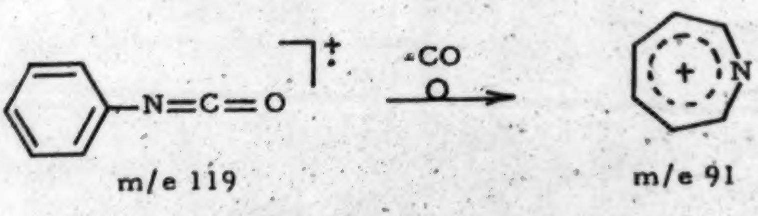

C6H5 +
n, m/e 77
CH3
O
+N=CH2
N
Ph
a, m/e 187
*
-H•
CH3
N——N-CH3
Ph
e, m/e 160
-CO
CH3
O
N
N
CH3
Ph
(329), M+•, m/e 188
-ĊH3
*
CH3
O
N
+N
Ph
b, m/e 173
-H
C10H11N2 +
f, m/e 159
*
* -PhṄH
-PhN=N-CH3
O
N
+ CH3
c, m/e 96
CH3
O
Ph
CH3
CH3
O
N≡N +
h, m/e 105
-CH3NC
C3H5O +
d, m/e 55
CH3
O
e, m/e 68
-HĊ NPh
O
-CO
CH3—N≡C—CH3 +
g, m/e 56
HC≡C—CH3 +•
m, m/e 40

Scheme 36

and led to appreciably abundant ions especially in the spectrum of aminopyrine (m/e 111; 17%). Both these $(M-120)^+$ ions fragmented further by the expulsion of a carbon monoxide molecule.

Another important fragmentation in the spectrum of antipyrine (329) was the formation of the phenyl diazonium cation h (Scheme 36) mostly from the $(M-CH_3)^+$ ion. Curiously, this was not demonstrated to any extent in the spectrum of aminopyrine in spite of structural similarities with antipyrine. Also, another minor ion (2%) corresponding to the expulsion of a CO molecule from the molecular ion of antipyrine was not present in the spectrum of aminopyrine. Similarly, a weak $(M-29)^{+}$ ion which may be due to the loss of $CHO^{\bullet}$ radical from the molecular ion or to the loss of $H^{\bullet}$ from the $(M-CO)^{+}$ ion was found in the spectrum of antipyrine, but not in the spectrum of aminopyrine. These findings indicated a lack of correlation between the fragmentation modes of these two compounds.

Some differences between a reported spectrum (Fig. 20) of aminopyrine (330) and those recorded here deserve comment. Tatematsu and Goto (1965) described a spectrum which contained a strong ion (95% relative intensity) at m/e 119. This ion was only present in 1% relative abundance under the conditions used in this study (70 eV and 110°). Changing the temperature did not seriously affect the intensity of this ion (5% at 165°). A spectrum of aminopyrine (330) recorded on a combined gas chromatograph/mass spectrometer* was also similar to the spectrum recorded in this study. Such an ion at m/e 119 may be attributed to the cleavage of the N—N bond with the formation of the phenyl isocyanate cation. The expulsion of a CO molecule from this cation could also explain the presence of a strong ion (46%) at m/e 91 in the spectrum reported by Tetamatsu and Goto (1965), and which was only 2-4% abundant in three spectra recorded for the present study.



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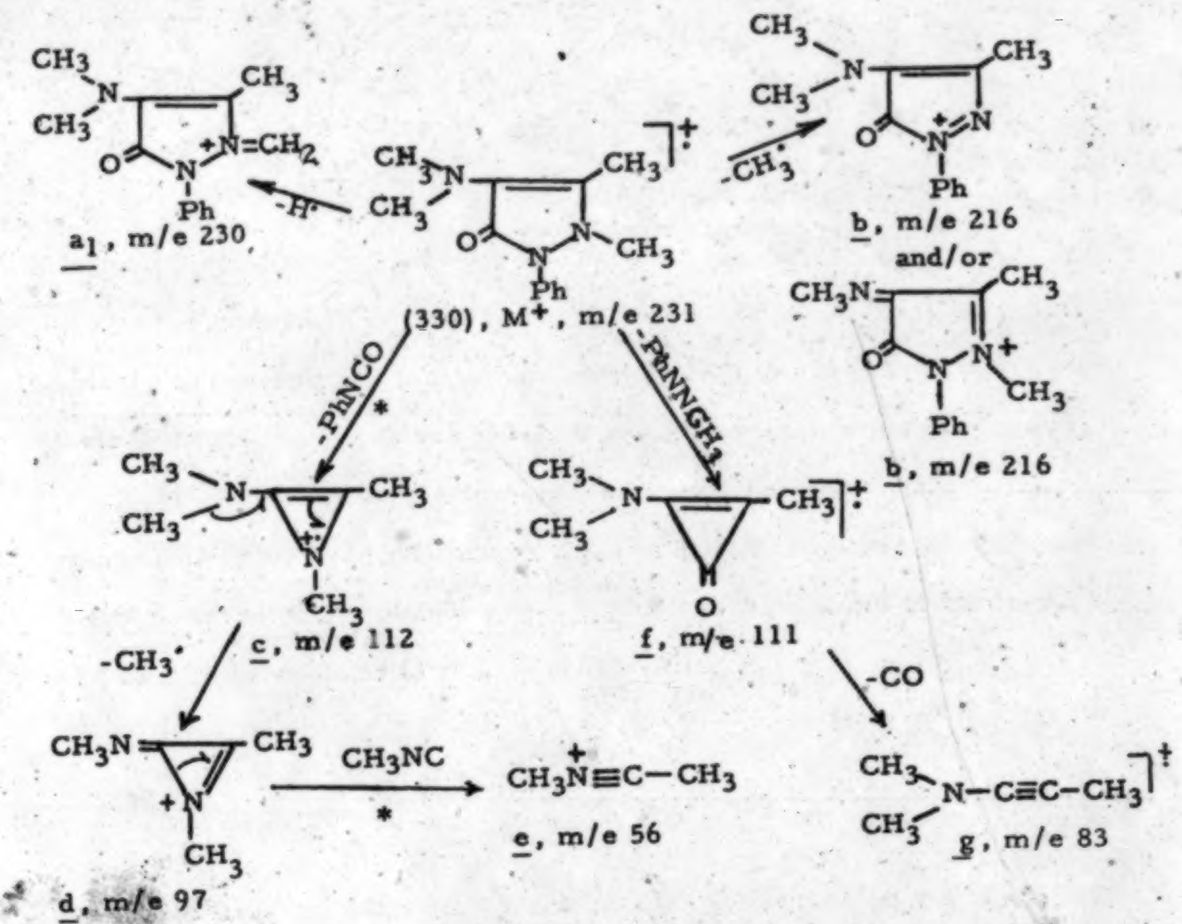
*recorded on a Perkin-Elmer model 270 combined gas chromatograph/ mass spectrometer at Chelsea College, University of London, England.


a1, m/e 230
-H·
(330), M+, m/e 231
-CH3·
b, m/e 216
and/or
b, m/e 216
-PhNCO
*
-PhNNCH3
c, m/e 112
f, m/e 111
-CH3·
-CO
CH3NC
*
$CH_3\overset{+}{N}{\equiv}C{-}CH_3$
e, m/e 56
g, m/e 83
d, m/e 97

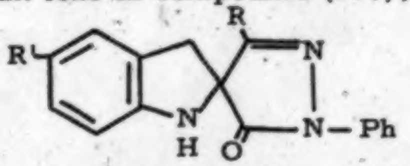
Scheme 37

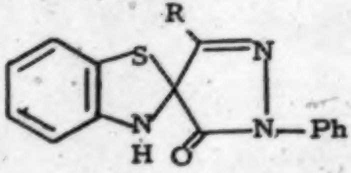
It is difficult to explain these gross differences except to suggest that aminopyrine fragments by alternative pathways depending on the conditions within the mass spectrometer.

- - - -

The spiro(indoline)pyrazolones (430) and the spiro(benzothiazoline)pyrazolones (431) displayed considerable similarities in their behavior under electron impact. However, some differences were also demonstrated either in the fragmentation pathways or in the intensity of the fragment ions produced. These differences are presumably due to the ability of compounds (431) to localize the charge on the sulfur atom and also due to the contribution of the methylene protons of the indoline ring in (430) to some of the fragment ions which are absent in (431).

The mass spectra of five spiro-(indoline)pyrazolone derivatives (430), one deuterated compound (339, D replaces H) and one acetylated compound (434) are shown in Fig. 21 and 22. The mass spectra of two spiro-(benzothiazoline)pyrazolones (431) as well as their deuterated derivatives (431), D replaces H) were also recorded (Fig. 23). Suggested fragmentation pathways of these two classes of compounds (430) and (431) are outlined in Schemes 39 and 40. Table 5 contains the mass measurements carried out on some of the important ions in compounds (339), (403) and (418).





(430); general structure

(339); R=CH_3, R'=H

(343); R=Ph, R'=H

(346a); R=CH_3, R'=Cl

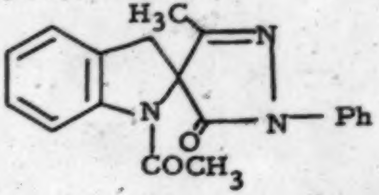
(346b); R=CH_3, R'=OCH_3

(346d); R=CH_3, R'=$OCOCH_3$

(431); general structure

(403); R=CH_3

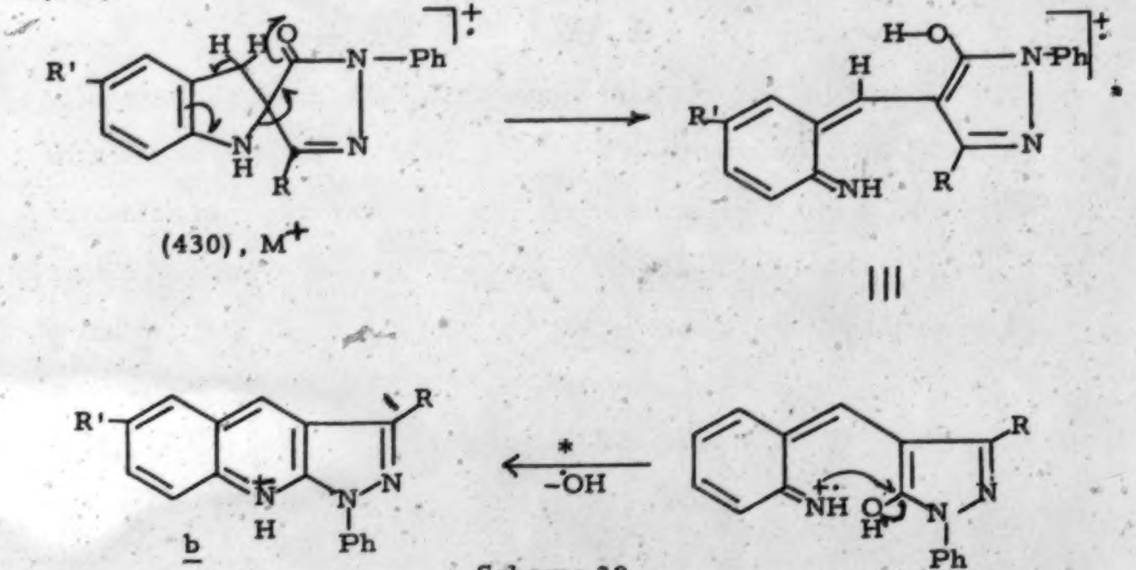
(418); R=Ph



(434)

All compounds (430) displayed strong $(M-1)^+$ ions (a) due to the loss of a hydrogen atom from the methylene group in the indoline ring. The fact that there was little or no contribution to this loss, from the C-methyl group in the pyrazolone ring was illustrated by the presence of a strong $(M-1)^+$ ion (21%) in the spectrum of (343) where no methyl substituent is present. Also, this ion was absent from the sulfur analogs (431). Additional evidence for the origin of this proton was found when the deuterated compound (339, D replaces H) was examined. It lost only one mass unit to provide the $(M-1)^+$ ion.

One of these methylene protons in (430) also contributes to the $(M-17)^+$ ion present in all the spectra of these compounds. An accurate mass measurement of this ion in compound (339) revealed that it was due to the loss of an $OH^\bullet$ radical from the molecular ion. Again, this ion was absent from the sulfur analogs (431). Deuterium labelling ruled out any contribution from the amine proton, since this ion at m/e 260 in (339) was located at m/e 261 in the deuterated compound. There is no evidence for the structure of the $(M-OH)^+$ ion, however, based only on the tentative mechanism illustrated in Scheme 38, it is identified as the ion (b). This $(M-17)^+$ ion was also present in the mass spectra of some spiro-(tetrhydroquinoline)pyrazolone derivatives (337) but not in the spiro (dihydrobenzothiazine)pyrazolones (419).



Scheme 38

Another important primary process demonstrated in the spectra of both compounds (430) and (431) was the expulsion of a carbon monoxide molecule from the molecular ions. In contrast to what was reported earlier by Maier et al (1969), the $(M\text{-}CO)^+$ ions produced here were present in appreciable intensity. The cyclic structures (c_2 in Scheme 39 and a_2 in Scheme 40), as well as open chain structures, can be suggested for this fragment. The former are in agreement with the commonly accepted cyclic structures for $(M\text{-}CO)^+$ ions in most organic compounds (Beynon et al, 1959; Bursey and Elwood, 1968).

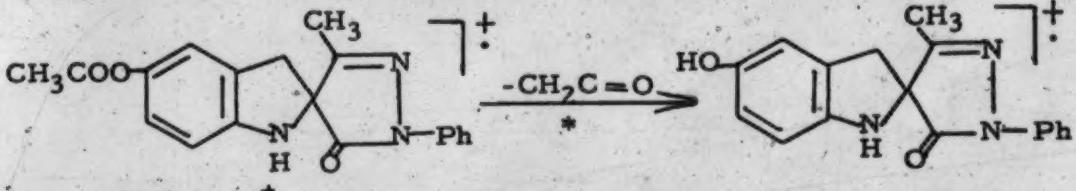
In the spiro-indoline derivatives (430), the $(M\text{-}CO)^+$ ions fragmented further by four different pathways which gave rise to many prominent ions in the spectra (see Scheme 39). Relatively weak ions are produced by the expulsion of CH_3CN or PhCN molecules from the $(M\text{-}CO)^+$ ions. On the other hand, the loss of $PhN_2^{\bullet}$ radicals from the $(M\text{-}CO)^+$ ions may be accompanied by ring expansion to give the stable ion j_1. The mode of formation of a relatively strong ion k is not clear but it might arise by the loss of a hydrogen atom from j. In compounds where $R=CH_3$, another loss of a hydrogen atom together with ring expansion could account for the presence of a relatively strong ion which is represented as m. Another major pathway is the decomposition of the $(M\text{-}CO)^+$ ion in two ways to give two strong ions g and f. The former expels an HCN molecule and the latter an RCN molecule to give ions h and i respectively.

The $(M\text{-}CO)^+$ ion in the spectra of spiro(benzothiazoline) pyrazolones (431) fragmented, with some exceptions, in a similar way. Here, the ion e, (which is analogous to g in Scheme 39), can fragment further by the expulsion of an HCN or DCN molecule or a CS molecule to yield ions g and f respectively. The $(M-CO)^+$ ion does not expel an RCN molecule as was demonstrated in (430).

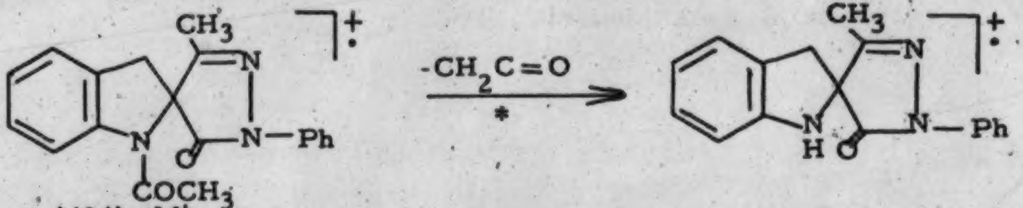
Several examples of primary and secondary processes where cleavage of the N–N bond occurs are demonstrated in the spectra of both the spiro (indoline)pyrazolones (430) and the spiro-(benzothiazoline)pyrazolones (431). The expulsion of a PhNCO molecule from the molecular ions of these compounds may be accompanied or followed by the loss of a methyl or phenyl radical; the loss of the former gives rise to relatively abundant ions. Abundant ion (n) in the spectra of the indoline derivatives (430) also formed either by the loss of a PhNCO molecule from the $(M-1)^+$ ions (a) or by the expulsion of PhNCO molecule followed by a hydrogen atom from the molecular ion. Another initial N–N bond scission accompanied by the expulsion of a methyl or phenyl cyanide molecule from the molecular ion is demonstrated in the mass spectra of both the methyl and phenyl analogs of the spirobenzothiaolines (431). In the spectra of the spiroindolines (430), this loss did not occur directly from the molecular ion but rather from the $(M-CO)^+$ ion.

Maier et al (1969), in a study of the mass spectra of some pyrazolone azomethine dyes, suggested that the very minor $(M-CO)^+$ ions found in these spectra, are intermediates in the formation of all the other major fragments. This suggestion was based on the finding that the carbonyl moiety was absent from all the major fragment ions. In our study, the $(M-CO)^+$ ions, which are present in appreciable intensities in the spectra of (430) and (431) were also deduced to be a major source of most of the fragment ions present. However, some other ions which incorporate the carbonyl moiety were also demonstrated. In the indoline derivatives (430), an accurate mass measurement of the ion at m/e 144 (12%) showed that 50% of this ion corresponds to the formulation C_9H_6NO, for which structure p is suggested (Scheme 39). Analogous ions ranging in intensity from 8 to 14% were also demonstrated in the spectra of (430b-e). The corresponding ion at m/e 162 in the mass spectrum of the sulfur analog (403) was found to be a singlet having the formulation C_9H_8NS and that ruled out the presence of a C=O group in this fragment ion. However, the ion at m/e 254 in the spectrum of (418) was shown by accurate mass measurement, to be solely due to the formulation $C_{14}H_{10}N_2OS$, which indicated the presence of C=O moiety in this fragment (b).

In addition to these common fragmentations, there are several fragments peculiar to some particular compounds. In the acetate derivatives (346d) and (434), the initial loss of a $CH_2{=}C{=}O$ molecule from the molecular ion makes a significant contribution to the overall fragmentation pattern. The $(M{-}CH_2CO)^+$ fragment ion in (434) decomposed under electron impact in a similar way to compound (339). On the other hand, other substituents made only a minor



(346a), M^+



(434), M^+

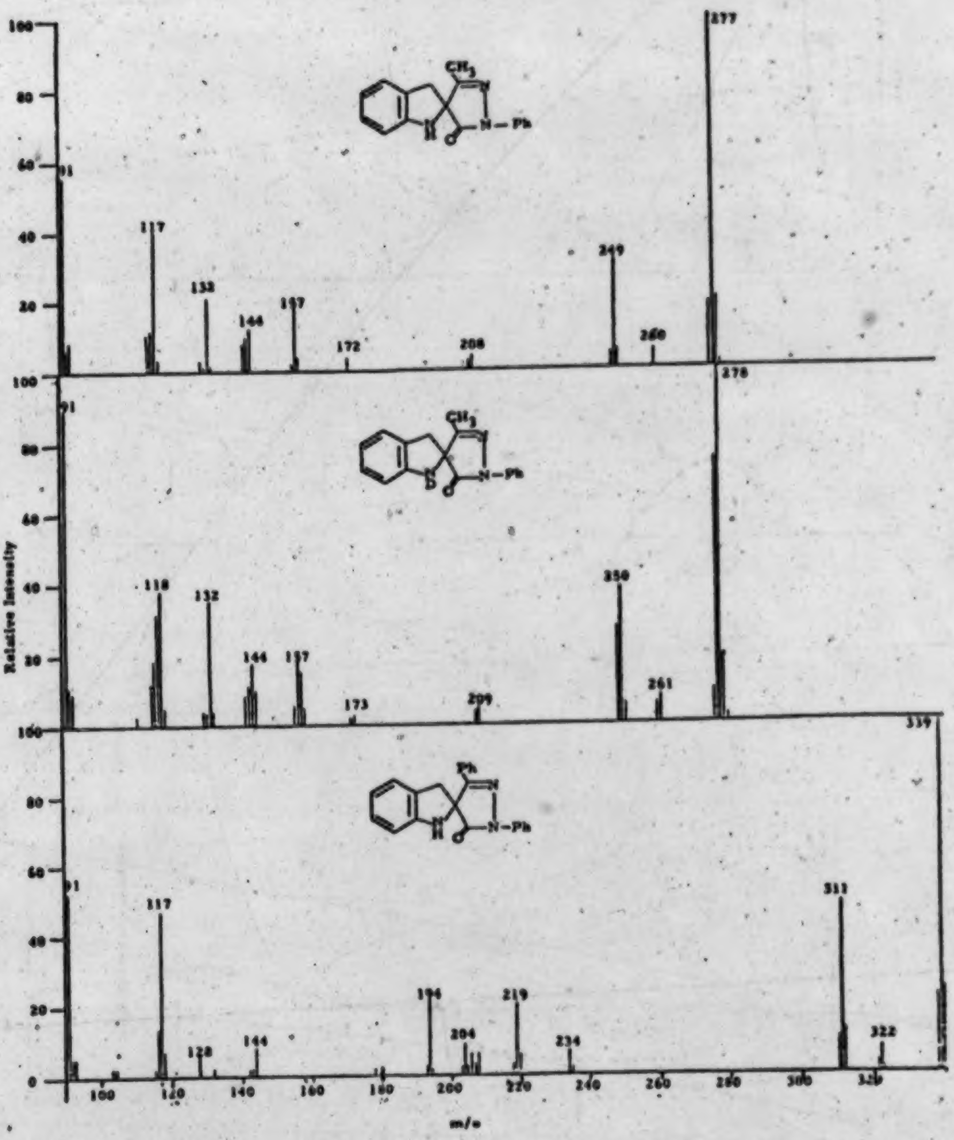


Fig. 21: Portions of the mass spectra of the spiro(indoline)pyrazolones (339), its deuterated derivative and the spiro(indoline)pyrazolone (343).

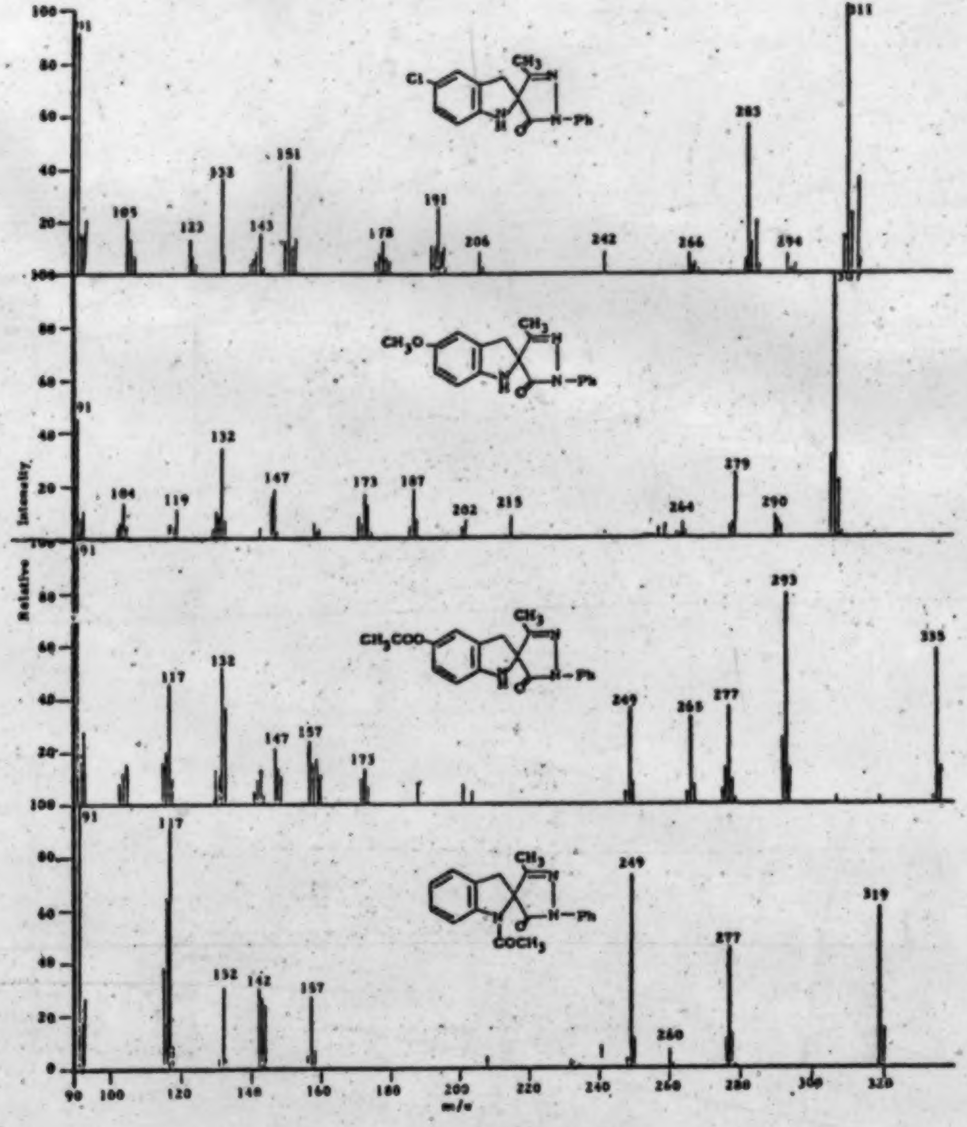


Fig. 22: Portions of the mass spectra of the spiro(indoline)-pyrazolones (346a, b, d and 434).

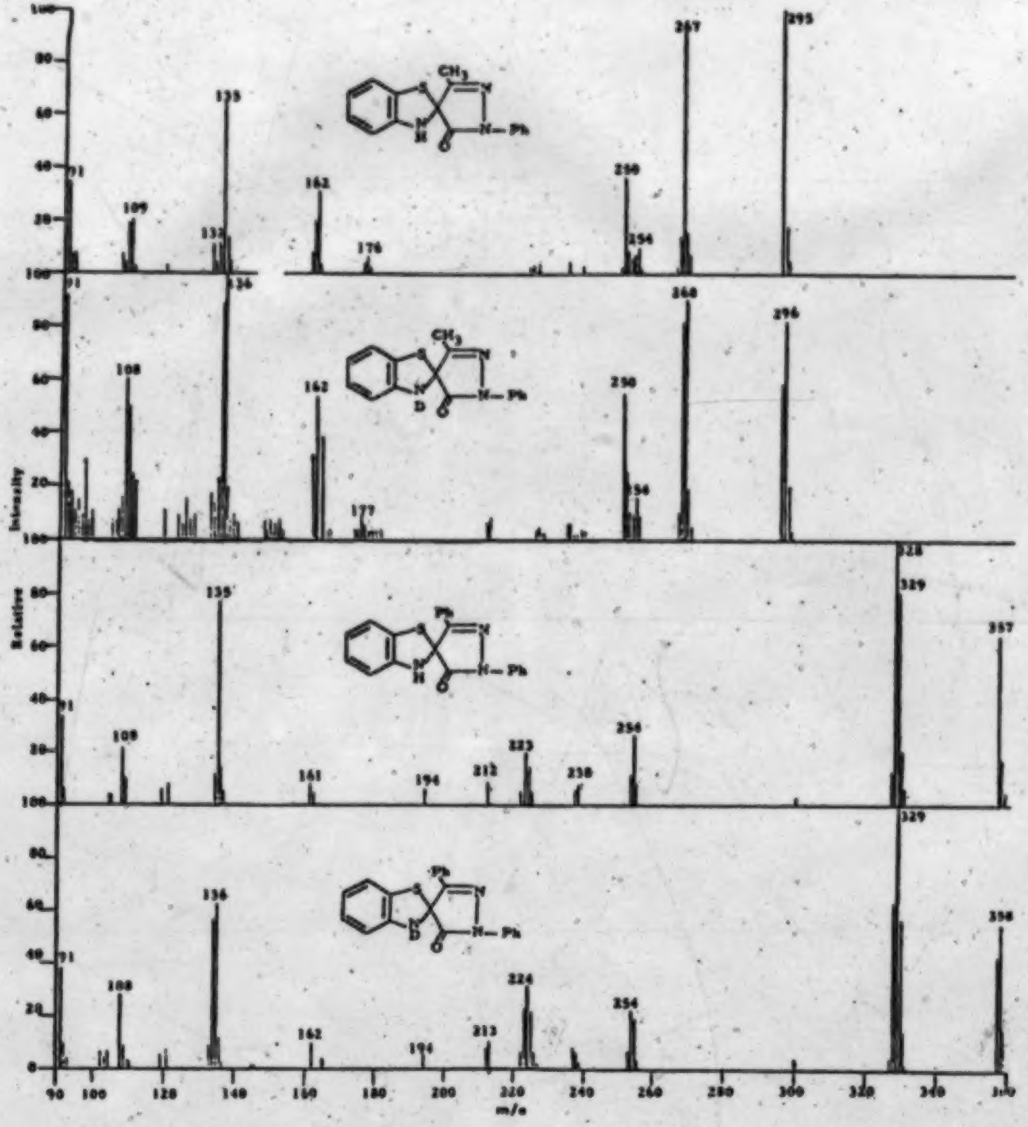
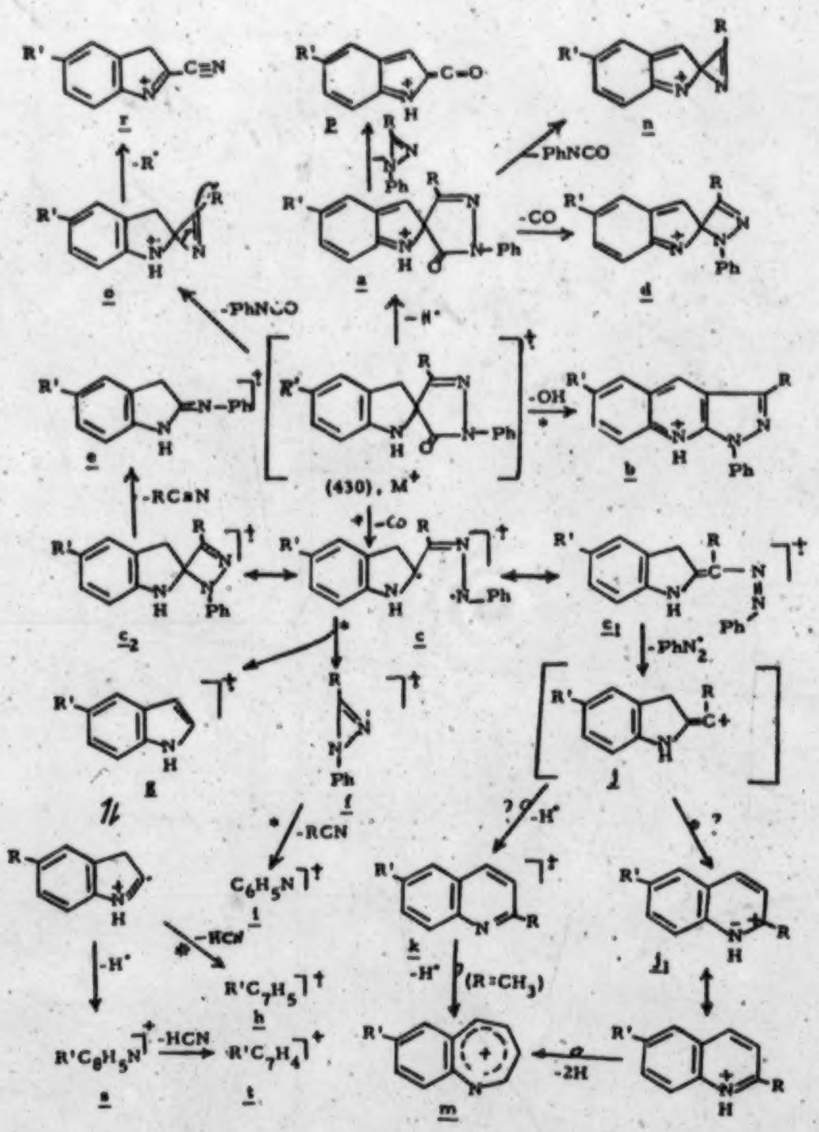
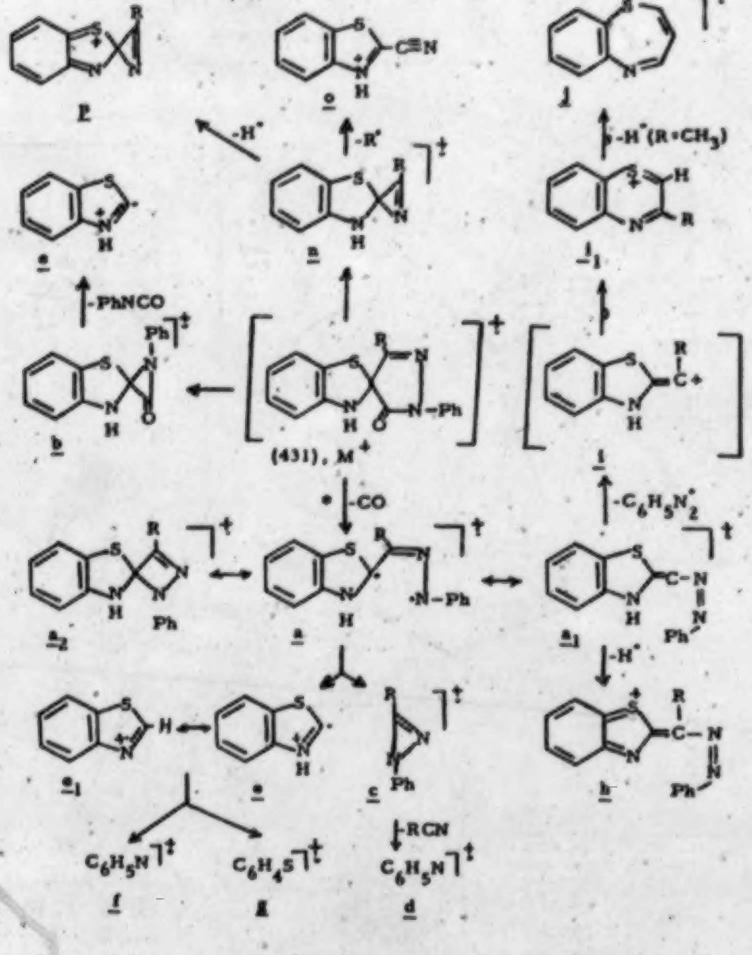


Fig. 23: Portions of the mass spectra of the spiro(benzothiazoline)-pyrazolones (403 and 418) and their deuterated derivatives.


r
p
n
-R'
-PhNCO
-CO
e
a
d
-PhNCO
-H'
(430), M+
-OH
b
e
-RC≡N
-CO
c2
c
c1
-PhN2+
g
f
j
-RCN
C6H5N
i
-RCN
? -H'
?
k
j1
-H'
(R=CH3)
R'C7H5
h
-HCN
R'C8H5N
s
R'C7H4
t
m
-2H

Scheme 39



p
o
j
-H˙
-R˙
-H˙(R=CH₃)
e
n
j₁
-PhNCO
b
(431), M⁺
i
-CO
$-C_6H_5N_2^{\cdot}$
a₂
a
a₁
-H˙
e₁
e
c
h
-RCN
C_6H_5N
f
C_6H_4S
g
C_6H_5N
d

Scheme 40

Table (5). Accurate Mass Measurement Data of some of the Important Ions in the Mass Spectra of the Spiro-pyrazolones (339), (403) and (418).*

Compound	Measured m/e	Composition	Required m/e	Designation†
339	260.1194	$C_{17}H_{14}N_3$	260.1188	b
	249.1270	$C_{16}H_{15}N_3$	249.1266	c
	157.0769	$C_{10}H_9N_2$	157.0766	n
	144.0816	$C_{10}H_{10}N$	144.0813	l
	144.0444	C_9H_6NO	144.0449	p
	132.0688	$C_8H_8N_2$	132.0688	f
	117.0581	C_8H_7N	117.0579	g
403	295.0781	$C_{16}H_{13}N_3OS$	295.0780	M^+
	267.0831	$C_{15}H_{13}N_3S$	267.0831	a
	250.0563	$C_{15}H_{10}N_2S$	250.0565	?
	162.0377	C_9H_8NS	162.0378	i
	161.0300	C_9H_7NS	161.0300	l
	161.0177	$C_8H_5N_2S$	161.0174	o
	135.0146	C_7H_5NS	135.0143	e
418	357.0935	$C_{21}H_{15}N_3OS$	357.0936	M^+
	329.0987	$C_{20}H_{15}N_3S$	329.0987	a
	328.0907	$C_{20}H_{14}N_3S$	328.0908	h
	254.0516	$C_{14}H_{10}NOS$	254.0514	b
	135.0143	C_7H_5NS	135.0143	e

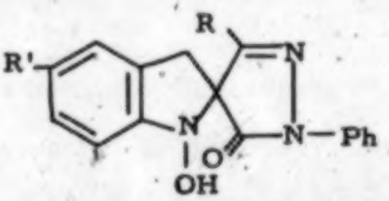
* only the important ions above m/e 117 were measured.

† as in Schemes 39 and 40.

contribution to the overall fragmentation patterns. For example, in the methoxy derivative (346b), the loss of a CH_3 radical from the molecular ion gave a weak ion (3%) at m/e 292 and the expulsion of a formaldehyde molecule (CH_2O) resulted in another ion (5%) at m/e 277.

(B) The Mass Spectra of Some Cyclic N-Hydroxy Compounds

Three spiro (N-hydroxyindoline)pyrazolones (435), two of their O-acetyl derivatives (436) and one O-methyl derivative (375) were prepared in this study and characterized by means of mass spectrometry. A literature search indicated that no detailed study of the effect of electron-impact upon cyclic N-hydroxy compounds had been reported. However, there are three isolated reports (Acheson et al, 1970; Beckett and Salami, 1972; Schweizer and Kopay, 1972) in which the presence of an $(m-17)^+$ ion in the spectrum was considered evidence of a cyclic hydroxylamine structure. To learn something of the mass spectral behavior of cyclic hydroxylamines and their N-acyloxy derivatives the spectra of simple reference compounds were examined initially. 1-Hydroxy-2-phenyl-1,2-dihydropyridine (255), its deuterated (255, D replaces H) and

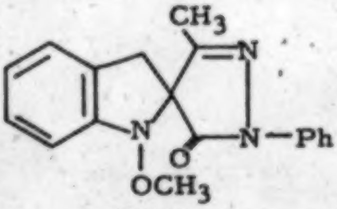


435, general structure

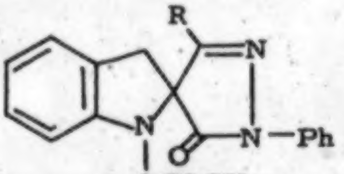
338; R=CH_3, R'=H

342; R=Ph, R'=H

347; R=CH_3, R'=Cl



(375)

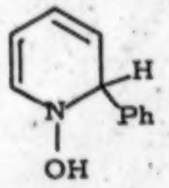


436, general structure

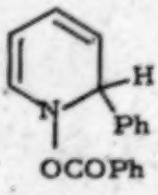
349; R=CH_3

361; R=Ph

O-benzoyl (437) derivatives were prepared by reported methods (Kato



(255)



(437)

and Yamanaka, 1965; Kato et al, 1967) and their mass spectra were recorded (Fig. 24).

The molecular ion of the N-hydroxy-1,2-dihydropyridine (255) expelled an $\dot{O}H$ radical to give ion of appreciable intensity at m/e 156 (Scheme 41). Also, due to the presence of a labile α-hydrogen atom in (255), a water molecule was expelled from the molecular ion giving rise to the molecular ion of 2-phenylpyridine. A weak fragment ion at m/e 157 might appear to be due to the loss of an oxygen atom, from the molecular ion of (255), but the absence of an equivalent ion at m/e 158 in the spectrum of the deuterated compound (255, D replaces H) indicated that this loss did not occur. The strongest fragment ion in the spectrum was formed by the expulsion, from the molecular ion, of the α-phenyl radical. The resulting ion at m/e 96 fragmented further by the expulsion of an $\dot{O}H$ radical and a water molecule; that the former was a direct fragmentation was inferred from the presence of a metastable ion at m/e 65.01.

In addition to these fragmentations which are illustrated in Scheme 41, the mass spectrum of (255) also displaced two relatively strong fragment ions at m/e 115 and m/e 102. The former ion is believed to be formed directly from the molecular ion as shown in

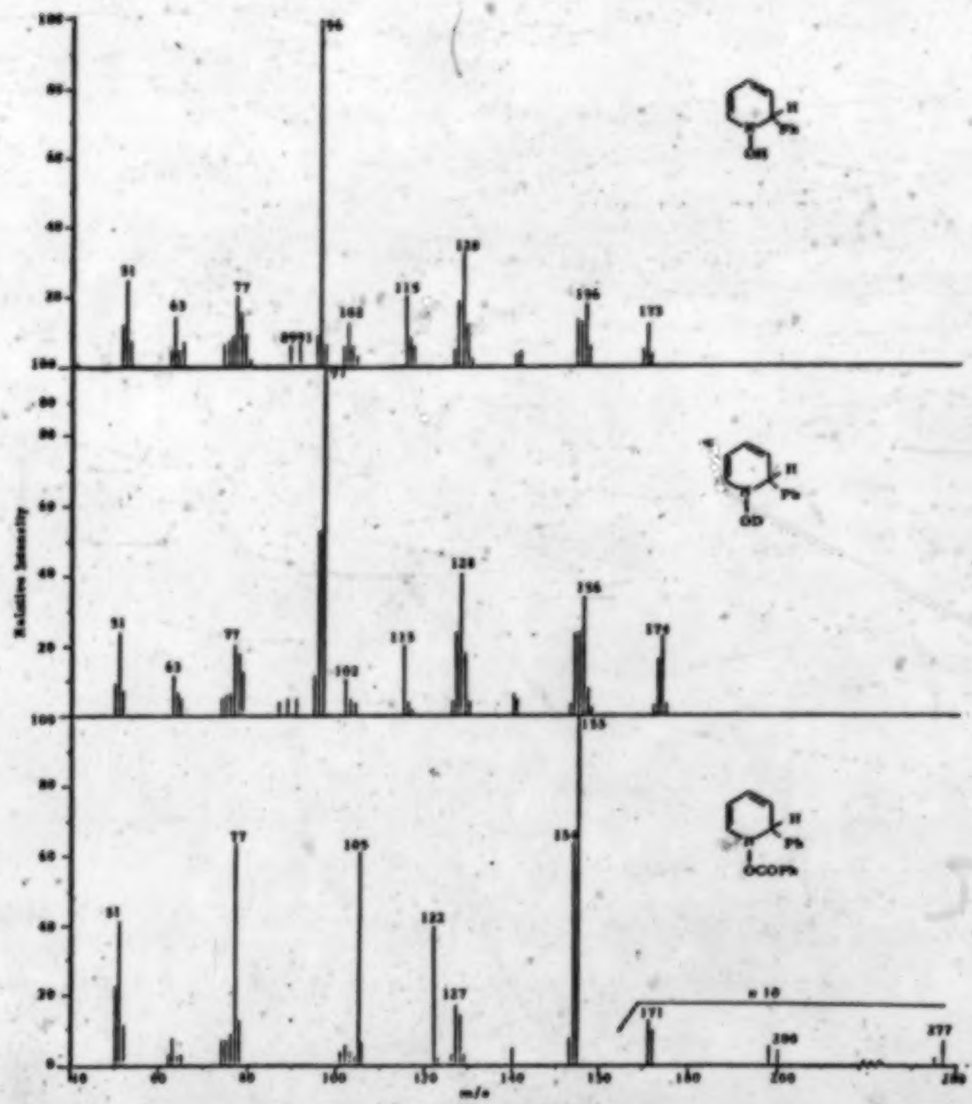
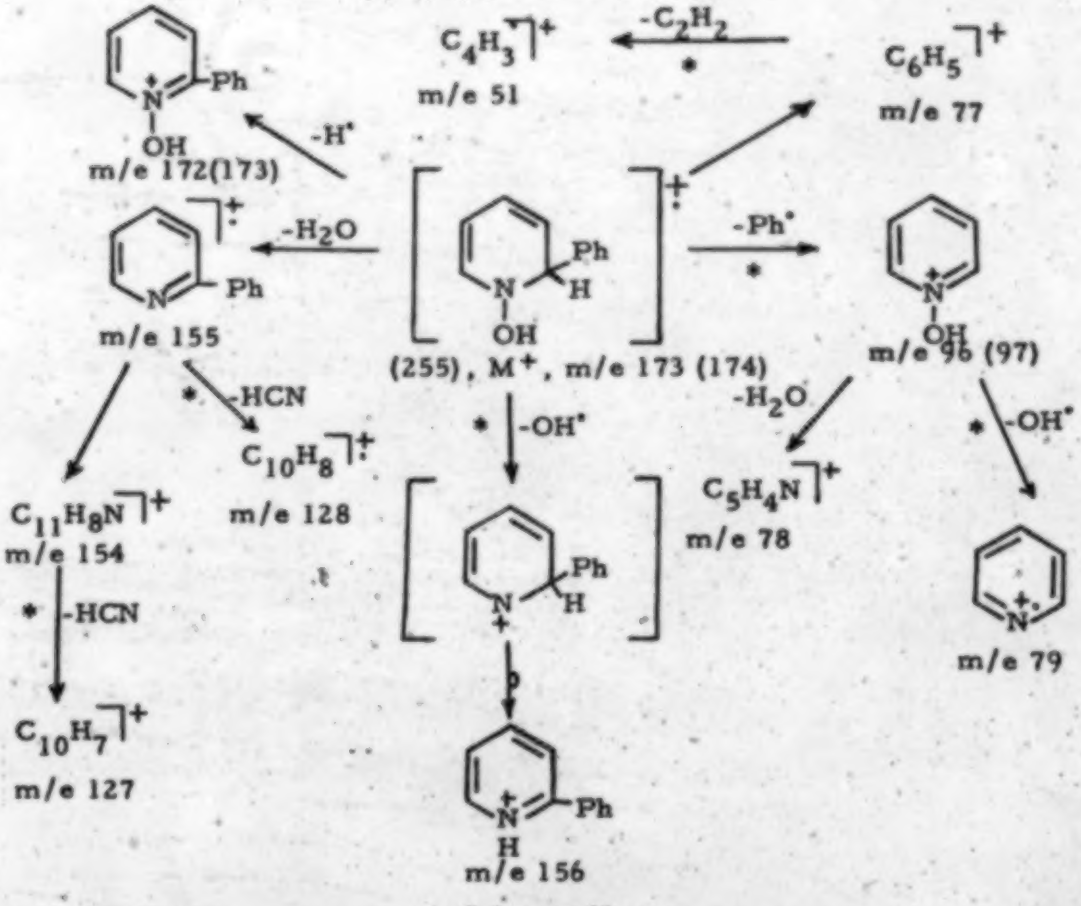


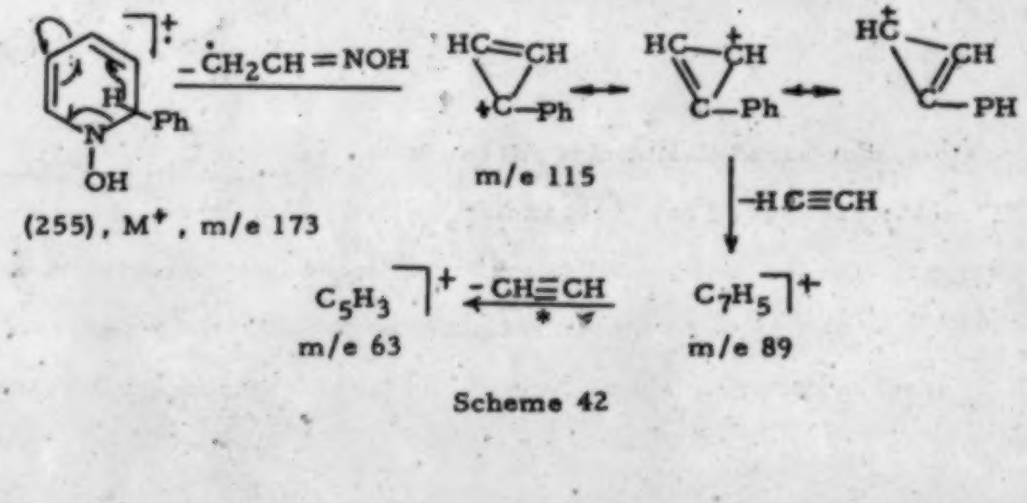
Fig. 24: **Portions of the mass spectra of 1-hydroxy-2-phenyl-1,2-dihydropyridine (255), its deuterated derivative and its benzoyl derivative (437).**



$C_4H_3^+$
m/e 51
$-C_2H_2$
*
$C_6H_5^+$
m/e 77
Ph
OH
m/e 172(173)
-H˙
Ph
m/e 155
$-H_2O$
Ph
H
OH
(255), M+, m/e 173 (174)
-Ph˙
*
OH
m/e 96 (97)
*
-HCN
$C_{10}H_8^{+\cdot}$
m/e 128
* -OH˙
$-H_2O$
$C_5H_4N^+$
m/e 78
* -OH˙
$C_{11}H_8N^+$
m/e 154
* -HCN
$C_{10}H_7^+$
m/e 127
Ph
H
m/e 79
Ph
H
m/e 156

Scheme 41

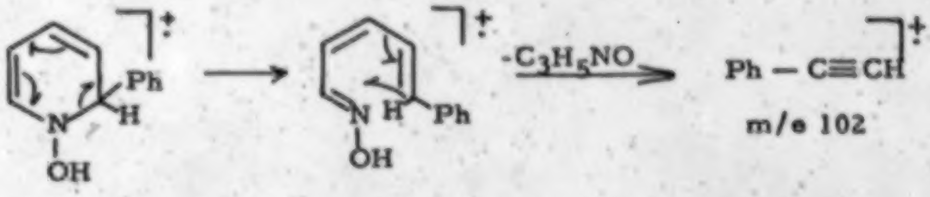
Scheme 42; this was supported by the presence of a metastable ion at m/e 76.45. It decomposed further by the ejection of two successive acetylene molecules to give ions at m/e 89 and m/e 63.



H
Ph
OH
(255), M+, m/e 173
$-\dot{C}H_2CH{=}NOH$
HC=CH
C—Ph
m/e 115
HC—CH
C—Ph
HC
CH
C—PH
—HC≡CH
$C_5H_3^+$
m/e 63
- CH≡CH
*
$C_7H_5^+$
m/e 89

Scheme 42

Fragmentation of the molecular ion in the manner shown in Scheme 43 might give rise to the ion at m/e 102, but no metastable was found to support this direct fragmentation.

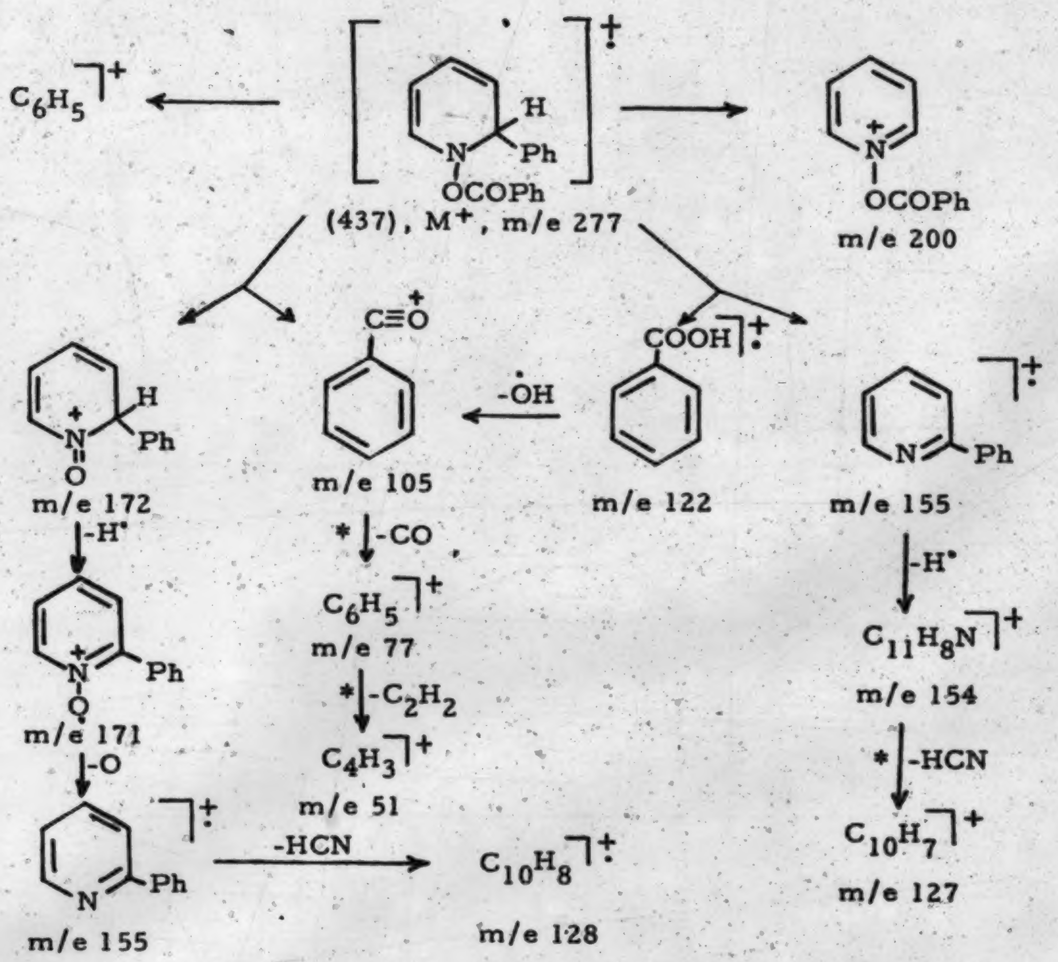


(255), M^+, m/e 173

Scheme 43

In the spectrum of the N-benzoyloxy derivative (437), the molecular ion and the fragment ion (m/e 200) resulting from the expulsion of the α-phenyl group were of low abundance. The base peak in (437) was formed by the ejection of a benzoic acid molecule to give the 2-phenylpyridine ion at m/e 155. This ion fragmented further by expelling an HCN molecule or a hydrogen atom followed by an HCN molecule. Charge retention on the benzoyloxy function also occurred as indicated by the strong ion at m/e 122 $(C_6H_5COOH)^+$. In addition, the molecular ion undergoes acyl-oxygen fission with charge retention on both the benzoyl portion and the pyridyloxy fragments. The former ion fragments further in predictable fashion (Scheme 44).

The mass spectra of the spiro-(N-hydroxy-indoline)-pyrazolones (435), their N-acetyloxy (436) and N-methoxy (375) derivatives are shown in Figs. 25 and 26. Although these spectra were complex, initial fragmentation could be interpreted and were very diagnostic and helped in the positive identification of these



C6H5 +
H
N
Ph
OCOPh
(437), M+, m/e 277
N+
OCOPh
m/e 200
C≡O+
COOH +
-OH
H
N+
Ph
O
m/e 172
m/e 105
m/e 122
N
Ph
m/e 155
-H•
* -CO
-H•
N+
Ph
O•
m/e 171
C6H5 +
m/e 77
* -C2H2
C4H3 +
m/e 51
C11H8N +
m/e 154
* -HCN
C10H7 +
m/e 127
-O
N
Ph
m/e 155
-HCN
C10H8 +
m/e 128

Scheme 44

compounds. The N-hydroxyindolines (435) displayed $(M)^+$ and $(M-1)^+$ ions, the abundance of which varied with the conditions in the mass spectrometer. In addition, abundant $(M-16)^+$ and $(M-17)^+$ ions were present in each of the spectra. These fragments correspond to the loss of an oxygen atom and a hydroxyl radical from the molecular ion. Strong metastables at appropriate m/e values in the spectra of (435) indicated that the transition $(M)^+ \longrightarrow (M-17)^+$ is direct. The expulsion of an oxygen atom from the molecular ions of cyclic N-hydroxy compounds has not been reported previously although Coutts

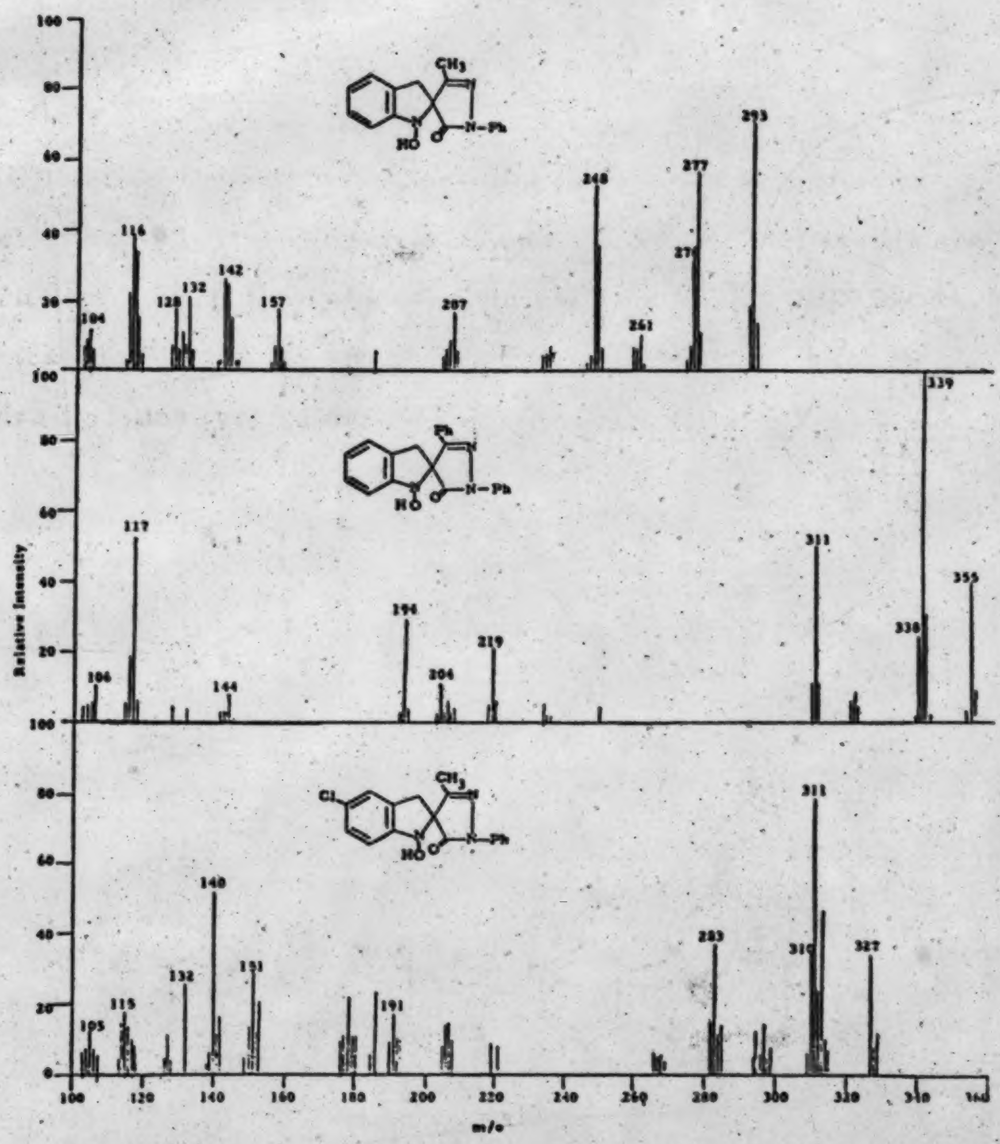
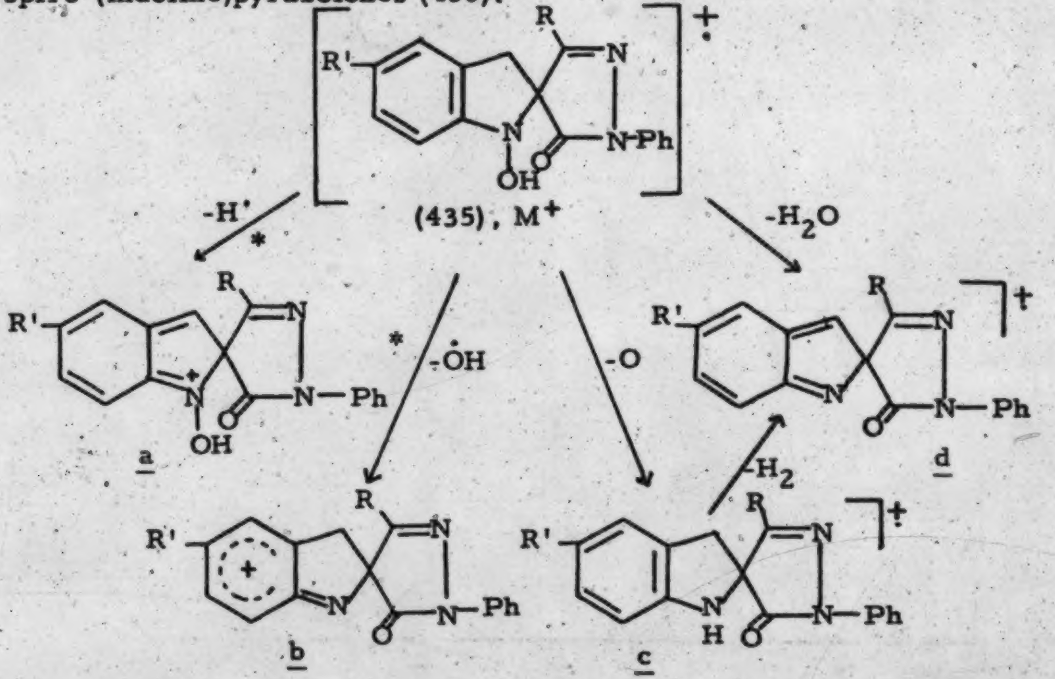


Fig. 25: Portions of the mass spectra of the spiro(N-hydroxyindoline)-pyrazolones (338, 342 and 347).

and Mukherjee (1970) have observed that aromatic hydroxylamines fragment by expelling an oxygen atom and a hydroxyl radical.

A relatively weak ion in the spectra of (435), which is identified in Scheme 45 as ion d, is due to the expulsion of a water molecule from the molecular ion; this expulsion might be direct or result from the successive losses of an oxygen atom and a hydrogen molecule. The other strong ions in the spectra of (435) are formed mainly by the expulsion of a CO molecule from the (M-OH)$^+$ ion or by fragmentation of ion c in the manner described earlier for the spiro (indoline)pyrazolones (430).



Scheme 45

Initial fragmentations of the N-acetyloxy derivatives (436) are illustrated in Scheme 46. Besides the expulsion of a ketene molecule to give ion a, each molecular ion also expelled a carbon monoxide molecule and gave the ion b. Further expulsion of a CO molecule from a or a $CH_2=C=O$ molecule from b produced a strong

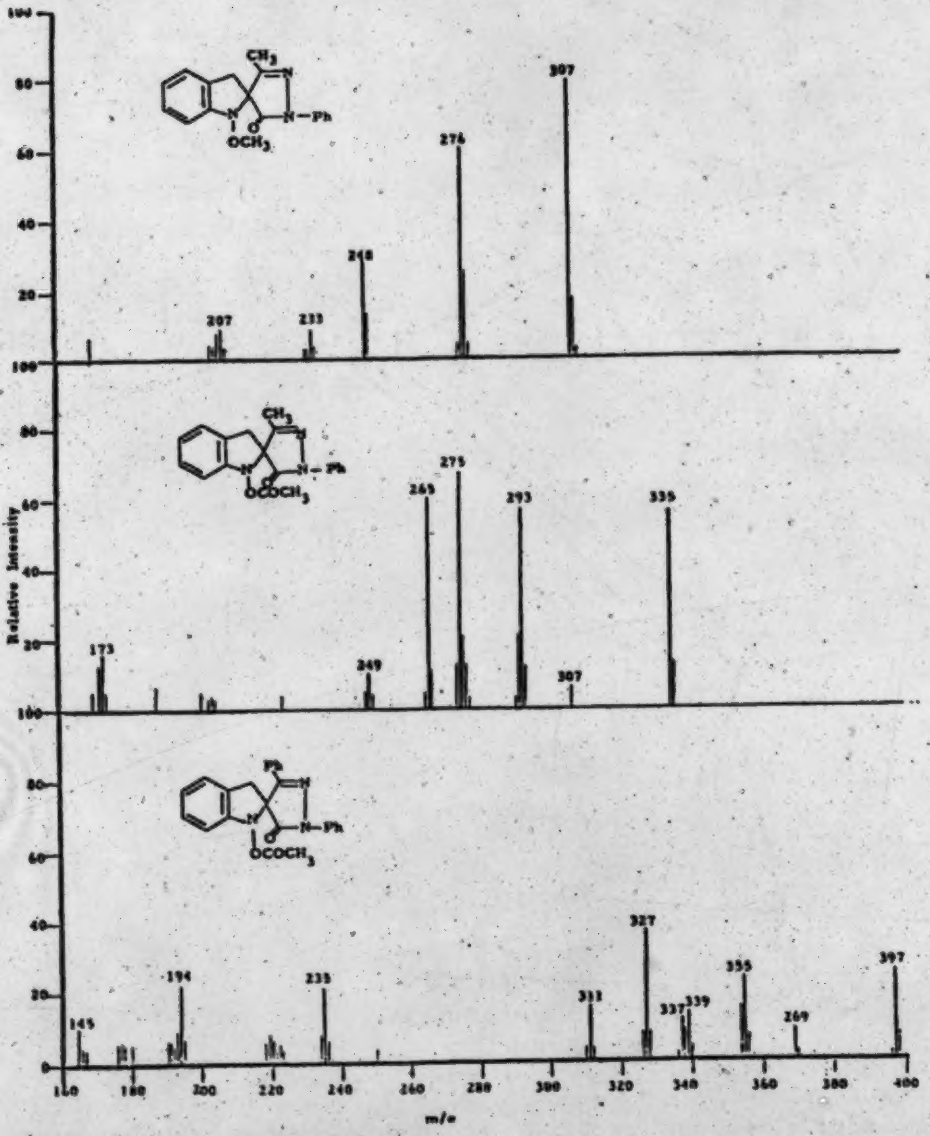
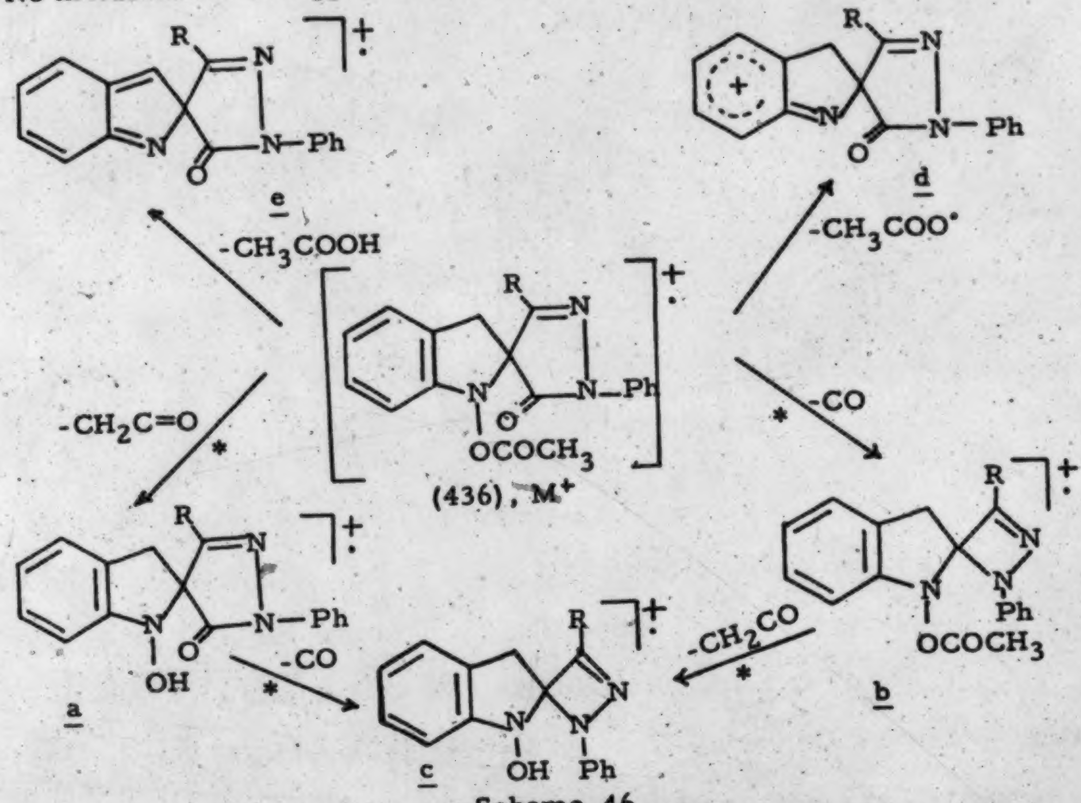


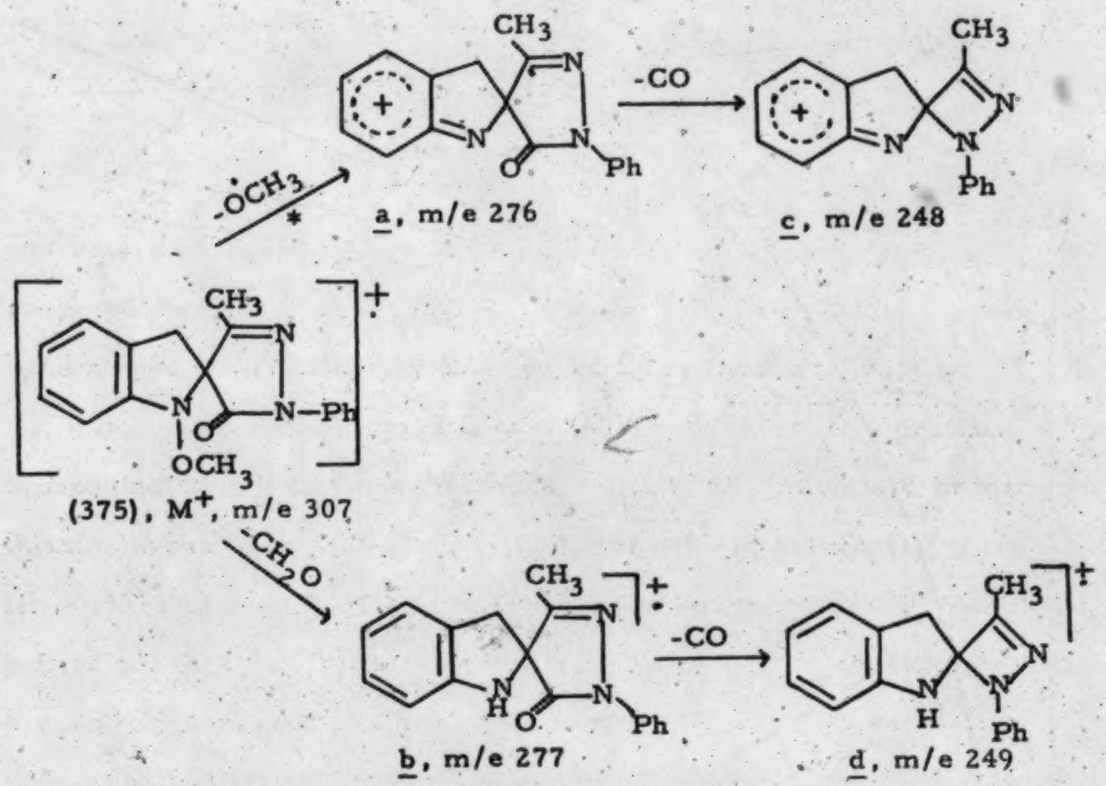
Fig. 26: Portions of the mass spectra of the spiro(N-methoxyindoline)-pyrazolone (375) and the spiro(N-acetyloxyindoline)pyrazolones (349 and 361).

ion tentatively identified as c. In addition, an $(M-59)^+$ ion and a strong $(M-60)^+$ ion are present in both spectra. These fragments might arise directly from the molecular ion by the expulsion of acetyloxy radicals and acetic acid molecules or, alternatively, by the loss of hydroxyl radicals and water molecules from the $(M-42)^{+}$ ions (a). No metastables to support either route were found in the spectra.


R
N
N–Ph
O
e
-CH3COOH
R
N
N–Ph
O
d
-CH3COO•
R
N
N–Ph
O
OCOCH3
(436), M+
-CH2C=O
*
-CO
*
R
N
N–Ph
O
OH
a
-CO
*
R
N
N
OH
Ph
c
-CH2CO
*
R
N
N
Ph
OCOCH3
b

Scheme 46

The mass spectrum of the N-methoxyindoline derivative (375) contained an abundant $(M-31)^+$ ion and a strong metastable ion at m/e 248.1 as a result of the expulsion of a methoxyl radical from the molecular ion. This is an interesting fragmentation; methyl ethers do not normally expel OCH_3 radicals except as a result of an ortho-effect displayed by some aromatic ethers (Cable et al, 1972; Coutts and Malicky, 1973). The mass spectrum of (375) also


CH3
-CO
-ȮCH3
*
a, m/e 276
c, m/e 248
Ph
(375), M+, m/e 307
OCH3
N–Ph
-CH2O
b, m/e 277
d, m/e 249
H

Scheme 47

contained an $(M-30)^+$ ion due to the expulsion of a formaldehyde molecule from the molecular ion (Scheme 47). The loss of a methyl radical, which generally occurs with aromatic methyl ethers, occurred with (375) only to a small extent. Both ions a and b in the spectrum of (375) fragmented further by expulsions of carbon monoxide molecules to give ions of appreciable abundance which are tentatively identified as c and d (Scheme 47).

A PRELIMINARY PHARMACOLOGICAL SCREENING OF SELECTED COMPOUNDS PREPARED IN THIS STUDY

To complete the objectives of this study, a preliminary pharmacological screening of some selected examples of the compounds prepared was undertaken. These were the spiro(N-hydroxyindoline) pyrazolones (338) and (342), the corresponding indolines (339) and (343), the spiro(benzothiazoline)pyrazolones (403) and (418), the spiro(tetrahydroquinoline)pyrazolones (337c,d,e,k,o,p), the spiro(dihydrobenzothiazine)pyrazolones (419c, e,h,j,k,l), the 4-(2-aminobenzyl)pyrazolones (321a,b) and their hydrochlorides, the 4-(2-aminophenylthio)-pyrazolone (416) and its hydrochloride, the 4-(2-mercaptophenylamino)-pyrazolone (406) and its dimethyl derivative (408). An observational technique similar to that described by Irwin (1962, 1964) was employed in an attempt to detect any behavioral, neurological or autonomic changes after administering each of the above compounds to mice. This random "screening" method was approached in view of the absence of guidelines to any "specific" activity to be expected from these diverse ring systems. However, because these compounds possess a 5-pyrazolone nucleus and thus bear some chemical similarity to the known analgesics, antipyrine, aminopyrine and nifenazone, all were also evaluated for their analgesic activity. A modification of the phenylquinone writhing test reported by Siegmund et al (1957) was used. It should be emphasized that the limitations and inadequacies of this method are well known.

METHODS:

A) For the general screening studies, Alas mice of either sex, weighing 18-24 g were used. About 12-16 hours before the experiment, the animals' diet was replaced with 20% glucose solution. Directly before being used, they were randomly divided into groups of six mice, three were administered each of the above compounds and three were used as a control and tested concurrently. The compounds to be tested were suspended in 1% gum tragacanth and were administered orally in a volume of 0.2 ml for each mouse. The initial dose for all compounds was 200 mg/kg and if an effect was produced, lower doses (150, 100, 50 . . . etc. mg/kg) were used until an ineffective dose was found. After administering the test compounds, the mice were placed in separate containers for 15 minutes then transferred to an observation chamber which had six separate compartments. A plexiglass wall allowed observation of the animals. Following a 10-minute observation period for general behavior and orientating movements, the three mice were put together, for five minutes, in an Animal Activity Cage (serial #A056, Woodard Research Corp.) which automatically recorded their movements. This was compared with that of the control mice. The mice were then removed from the cage and a number of neurological reflexes (e.g. righting, grasping, ... etc.) tested. Notations were also made of animals motor activity, general appearance and behavior. At regular intervals for two hours, these tests were repeated. The animals were then transferred to cages (three in each) and kept under observation for five days where death, if any, was recorded.

At a later stage, some of the above test compounds [the spiro(N-hydroxyindoline)pyrazolones (338) and (342), the spiro-

(indoline)pyrazolones (339) and (343) and the amine (421a)] were administered intraperitoneally to the mice at different dose levels and the animals gross behavior was observed. Standard drugs were also given to some groups of mice when comparisons were required.

B) For the analgesic studies, female Alas mice, 17-23 g in weight were brought to this laboratory about 7 days before being used and kept on a standard diet. About 12 hours before the experiment, the food was replaced with 20% glucose solution. The animals were divided at random into groups of five mice then each group was dosed orally with one of the test substances (prepared as suspensions in 10% polysorbate 80 U.S.P. and given at initial dose of 200 mg/kg, in a volume not exceeding 0.1 ml/10 g of body weight). Twenty-five minutes later, each mouse was injected intraperitoneally with 0.25 ml of 0.02% phenylquinone(2-phenyl-1,4-benzoquinone, Eastman Organic Chemicals) in 5% alcohol (this solution was prepared daily and kept in amber bottle at 37° to prevent its deterioration). The mice were then placed in observation boxes and the number of writhes occurring in a 10-minute period, starting five minutes after injection, were counted for the group of five mice.

A number of control experiments were performed every day the experiment was done. These data were pooled and an average control level determined. A standard drug, aminopyrine, was administered orally in four dose levels (200, 150, 100, 50 mg/kg) to groups of five mice each then these mice were challenged with phenylquinone 25 minutes later.

The percent protection afforded by each substance was determined for each experimental group of five mice as follows:

$$\% \text{ protection} = 100 - \left(\frac{\text{experimental}}{\text{control}} \times 100\right)$$ (Hendershot and Forsaith,

1959).

RESULTS:

A) The general screening studies showed that up to an oral dose of 200 mg/kg, most of the above compounds demonstrated only a weakly sedative effect in mice. Included are the spiro N-hydroxyindoline (338) and (342) which showed at this dose level some decrease in motor activity and degree of alertness. Giving this dose intraperitoneally led to no increase in these effects. On the other hand, the spiro indolines (339) and (343) demonstrated some neuroleptic properties which significantly increased when these compounds were given intraperitoneally. At an oral dose of 100 mg/kg and over, compound (339) caused a marked decrease in motor activity, reactivity and alertness, and some muscle relaxation. These symptoms were comparable to those obtained when the same compound was given intraperitoneally to mice in a dose of 50 mg/kg. Below an oral dose of 100 mg/kg or an i.p. dose of 50 mg /kg, no effects were seen. Similar signs were obtained when chlordiazepoxide was administered i.p. in a dose of 50 mg/kg except in this case, ptosis and more muscle relaxation were observed.

The 4-(2-aminobenzyl)pyrazolone (321a) demonstrated, at an oral dose of 100 mg/kg and up, hypnotic properties marked by a preliminary excitation period then depression and sleep. A similar effect was observed when sodium pentobarbital was administered orally to mice in a dose of 50 mg/kg. The mice given compound (321a) recovered after 1-2 hours while those given the barbiturate derivative took 3-4 hours to recover. The hypnotic effect was not demonstrated below an oral dose of 50 mg/kg and was not prolonged by giving the compound intraperitoneally.

At oral or intraperitoneal dose levels of 200 mg/kg and below, none of the compounds tested produced any gross toxicity.

B) Of all the compounds tested, only the spiroindolines (339) and (343) showed weak analgesic activity when administered orally to the test mice. A decrease in the total number of writhes as compared with the controls was observed at oral doses of 200 and 100 mg/kg for (339) and 200 mg/kg for (343), but no effect was noted below this dose level. The percent protection was small, 48% and 34% for the two dose levels of (339) and 45% for the dose level of (343) as compared with 94% and 59% protection given by oral doses of 200 and 100 mg/kg of aminopyrine. Since the effects observed for the test compounds were weak, no attempts were made to administer other dose levels in order to calculate their ED_{50}.

From the results obtained, it is evident that these compounds have relatively weak neuroleptic properties. These weak properties may be due in part to the low solubility of these compounds in water.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus. All melting points quoted are uncorrected. Infrared (i.r.) spectra were recorded on a Beckman IR-10 spectrophotometer; nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A-60 spectrometer and chemical shifts are recorded in ppm (δ) down field from tetramethylsilane (TMS). Mass spectra were determined by Dr. A. M. Hogg and his associates, Department of Chemistry, University of Alberta, with an AEI MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct Probe technique. Elemental analyses were performed by the microanalytical laboratories of the Faculty of Pharmacy and Pharmaceutical Sciences and the Department of Chemistry, University of Alberta.

The following abbreviations will be used throughout this section:

br = broad
d = doublet
m = multiplet
q = quartet
s = singlet
t = triplet

I. REDUCTIONS OF 4-(2-NITROBENZYLIDENE)-2-PYRAZOLINE-5-ONES

1,3-Diphenyl-2-pyrazolin-5-one (317b)

This compound was prepared following the procedure reported by Hinton and Mann (1959). Phenylhydrazine (11.9 g) was slowly added to ethyl benzoylacetate (21.4 g) and the mixture warmed on a water bath for five minutes. This solution was then poured into ether (75 ml) and stirred for two hours. The title compound, which precipitated slowly during this time, and was collected and recrystallized from ethanol to yield an off-white solid (19.3 g), m.p. 135-7°. Reported (Hinton and Mann, 1959) m.p. 135-8°.

3-Methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a) (Coutts and Edwards, 1966).

A mixture of o-nitrobenzaldehyde (6.7 g), 3-methyl-1-phenyl-2-pyrazolin-5-one (7.0 g), fused sodium acetate (3.8 g), and acetic anhydride (12 ml) was heated on a water-bath until a homogenous red solution formed. When cooled, a dark-red crystalline product was formed. This was washed with water then with cold ethanol and recrystallized from ethanol to give the title compound (8.2 g) as orange-red crystals, m.p. 162-3°. Reported m.p. 162° (Narang et al, 1934), 160-2° (Coutts and Edwards, 1966).

I.r. spectrum (nujol): 1688 (C=O); 1522 and 1337 (NO_2) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.35 (3H, s, CH_3); 7.0-8.4 (10H, m, aromatic protons).

The following compounds were prepared in a similar manner:

1,3-Diphenyl-4-(2-nitrobenzylidene)-2-pyrazolin-5-one (318b) was obtained as red needles (9.9 g, m.p. 180-2°) from o-nitrobenzaldehyde (6.0 g) and 1,3-diphenyl-2-pyrazolin-5-one (10.0 g). Reported (Coutts and Edwards, 1966) m.p. 181-2°.

I.r. spectrum (nujol): 1695 (C=O); 1540 and 1330 (NO_2) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ6.9-8.4 (15H, m, aromatic protons).

4-(5-Chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (318c) was obtained as orange-red needles (5.1 g, m.p. 141-2°) from 3-chloro-6 nitrobenzaldehyde (7.4 g) and 3-methyl-1-phenyl-2-pyrazolin-5-one (7.0 g). Reported (Coutts and Edwards, 1966) m.p. 140-2°.

I.r. spectrum (nujol): 1695 (C=O); 1520 and 1333 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.35 (3H, s, CH_3); 7.0-8.6 (9H, m, aromatic protons).

General Procedure for sodium borohydride and palladium-charcoal reductions.

A solution of sodium borohydride (0.5 g) in water (10 ml) was carefully added to a suspension of palladium-charcoal (0.05 g) in water (5 ml). The nitro compound (1.0 g), dissolved in a suitable solvent, was added dropwise over a period of thirty minutes. Nitrogen was bubbled through the reaction mixture during the addition of the nitro compound and for a further fifteen minutes. The mixture was then filtered and the filtrate acidified and diluted with ice-cold water. The precipitated product was either filtered off or extracted into ether.

Reductions of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a).

Method A: Reduction with sodium borohydride in dioxane

The title compound (4.0 g) in dioxane (80 ml) was added dropwise to a stirred solution of sodium borohydride (2.0 g) in 50% aqueous dioxane (20.0 ml). After addition was completed, stirring was continued for one hour. The reaction mixture was cooled and acidified with dilute hydrochloric acid then diluted with water. The precipitate was collected and crystallized from ethanol to give a yellow crystalline compound (3.4 g) m.p. 168-9° which was identified as 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (319a).

I.r. spectrum (nujol): 2300-3200 v. br. (OH); 1605 (C=N); 1530 and 1335 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ 2.05 (3H, s, CH_3); 3.95 (2H, s, CH_2); 7.4 (1H, br., exchanged with D_2O, OH); 7.1-8.1 (9H, m, aromatic protons).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.88; N, 13.58.
Found: C, 65.91; H, 5.00; N, 13.39.

Method B: Reduction with sodium borohydride and palladium-charcoal in dioxane:

(i) Using the general procedure (p. 245), a solution of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a) (3.0 g) in dioxane (50 ml) was reduced with sodium borohydride and palladium-charcoal. When the filtered reaction mixture was acidified with dilute hydrochloric acid then flooded with water (300 ml), it yielded a dark yellow precipitate (2.8 g). Attempts to purify the crude product by crystallization proved difficult. Chromatography on a silica gel column using chloroform/ether (9:1) followed by evaporation of eluate gave a yellowish crystalline compound (1.2 g), m.p. 187-8° d. (ethanol) which was identified as spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (338). This compound reduced Tollen's reagent and gave, in the presence of alkali, a purple-red color with triphenyltetrazolium chloride.

I.r. spectrum (nujol): 1690 (C=O); 3275, br. (N–OH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ1.97 (3H, s, CH_3); 3.28 (2H, br, CH_2); 9.67 (1H, br, exchanged with D_2O, N–OH); 6.7-8.1 (9H, m, aromatic protons).

N.m.r. spectrum (pyridine): δ2.1 (3H, s, CH_3); 3.44 (2H, doublet of doublets, J=16 Hz, CH_2); 12.1 (1H, br. exchanged with D_2O, N–OH); 7.1-7.8 (9H, m, aromatic protons).

Mass spectrum: See Fig. 25.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.16; N, 14.33.
Found: C, 69.62; H, 5.07; N, 14.29.

Further elution of the column with more polar solvent yielded only small amounts of dark brown oils which were not investigated.

(ii) When the above reaction was repeated and the filtered reaction mixture was acidified with dilute acetic acid then flooded with ice-cold water (300 ml), it gave a white precipitate. Crystallization from ethanol offered a white crystalline product (1.5 g) melted at 191-2° (decomp.). Infrared and n.m.r. spectra were identical to those of the N-hydroxyindoline described above. Concentration of the mother liquor yielded a white crystalline second product (0.4 g), m.p. 152-3°. This was 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a). Reported m.p. 141-2° (Coutts and Edwards, 1966), 142° (Narang *et al*, 1934) (Compound erroneously identified by these authors).

I.r. spectrum (nujol): 1628 (bonded C=O); 1604 (C=N); broad absorption between 2100 and 3500 with maxima at 3200; and 3345 (OH and

NH_2) cm^{-1}.

I.r. spectrum ($CHCl_3$, 2% solution): 1712 (C=O) cm^{-1}.

I.r. spectrum (DMSO, 2% solution): 1660, average (C=O); 1603 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.1 (3H, s, CH_3); 3.43 (2H, s, CH_2); 6.3-7.9 (12H, m, aromatic protons included 3 exchanged with D_2O for NH_2 and pyrazolone proton).

N.m.r. spectrum ($CDCl_3$): δ1.19 (3H, s, CH_3); 3.3(2H, s, CH_2); 6.5-8.2 (9H, m, aromatic protons); 6.0-6.5 (3H, br., exchanged with D_2), NH_2 and pyrazolone proton).

Mass spectrum: See Fig. 1 .

Accurate mass measurements: 186.0790, $C_{11}H_{10}N_2O$ requires 186.0793; 106.0655, $C_6H_6N_2$ requires 106.0657.

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04.

Found: C, 73.08; H, 6.08; N, 14.91.

(iii) Reduction of the nitrobenzylidene derivative (318a) with sodium borohydride and palladium-charcoal was repeated as above and the filtrate was diluted with ice-cold water before acidification. A white precipitate (1.6 g) formed and was collected and crystallized from ethanol to give the previously identified spiro(N-hydroxyindoline) pyrazolone (338), m.p. 192-3°. The filtrate from this was then acidified with glacial acetic acid to give a white precipitate (0.5 g) which was crystallized from ethanol into a small amount (0.08 g) of white crystals identified as spiro[(indoline)-2,4'(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (339), m.p. 126-7°.

I.r. spectrum (nujol): 1725 (C=O); 3305 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.09 (3H, s, CH_3); 3.33 (2H, doublet of doublets, J=16.5 Hz, CH_2); 5.57 (1H, br., exchanged with D_2O, NH); 6.56-8.1 (9H, m, aromatic protons).

Mass spectrum: See Fig. 21.

Accurate mass measurements: See Table 5.

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15.

Found: C, 73.93; H, 5.49; N, 14.94.

The mother liquor remaining after the removal of the above product was concentrated to yield a third product (0.33 g), m.p. 153-4° which was found to be the 4-(2-aminobenzyl)pyrazolone (321a). Its infrared spectrum was identical with that of an authentic sample of (321a).

Method C: Reduction with sodium borohydride and palladium-charcoal in methanol.

Following the general procedure outlined above (p. 245), a solution of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (2.0 g) in methanol (120 ml) was reduced with catalyzed (10% Pd-C) sodium borohydride. The reaction mixture was filtered and the filtrate was acidified with glacial acetic acid. A small amount (0.13 g) of a pale-yellow product, m.p. 146-9° was deposited. This was collected and recrystallised from ethanol to give a white crystalline compound, m.p. 182-3° identified (i.r. and n.m.r.) as the spiro(N-hydroxyindoline)pyrazolone (338). When the filtrate remained after collecting this product was concentrated and allowed to stand, it yielded a crystalline product (0.63 g), m.p. 151-2° which was identical to the 4-(2-aminobenzyl) pyrazolone (321a) described above.

Reductions of 1,3-diphenyl-4-(2-nitrobenzyliden)-2-pyrazolin-5-one (318b).

Method A: Reduction with sodium borohydride in dioxane.

The title compound (3.0 g) was reduced with sodium borohydride (1.5 g) as described for the reduction of the methyl analog (318a) (method A). The resulting yellow precipitate was crystallized from ethanol as a pale-yellow solid (2.7 g), m.p. 185-6°. This was identified as 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (319b).

I.r. spectrum (nujol): 2400-3200 br. (OH); 1604 (C=N); 1527 and 1340 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ4.2 (2H, br. s, CH_2); 7.8 (1H, br. s, exchanged with D_2O, OH); 7.1-8.1 (14H, m, aromatic protons).

Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31.

Found: C, 71.30; H, 4.41; N, 11.24.

Method B: Reduction with sodium borohydride and palladium-charcoal in dioxane.

1,3-Diphenyl-4-(2-nitrobenzylidene)-2-pyrazolin-5-one (3.0 g) was reduced according to the general procedure using dioxane (60 ml) as solvent. The reaction mixture was filtered and the filtrate acidified with dilute acetic acid then flooded with ice-cold water (300 ml). The precipitate formed was crystallized from ethanol into an off-white solid (1.2 g), m.p. 178-9° (decomp.) which was identified as spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (342). This compound reduced Tollen's reagent and gave postive tests with triphenyltetrazolium chloride.

I.r. spectrum (nujol): 1696 (C=O); 3347 (N–OH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ3.47 (2H, br. s, CH_2); 9.8 (1H, br. s, exchanged with D_2O, N-OH); 6.7-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 25.

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.79; N, 11.82.

Found: C, 74.23; H, 4.87; N, 11.89.

Concentration of the mother liquors after the removal of the above product gave 0.35 g of second compound, 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b), m.p. 151-3°. Reported (Coutts and Edwards, 1966) m.p. 109-10° (compound erroneously identified by these authors).

I.r. spectrum (nujol): 1625 (bonded C=O); 1600 (C=N); 2200-3400 broad with maxima at 3170 and 3350 (OH and NH_2) cm^{-1}.

I.r. spectrum ($CHCl_3$, 2% solution): 1711 (C=O) cm^{-1}.

I.r. spectrum (DMSO, 2% solution): 1654, average (C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ3.68 (2H, s, CH_2); 6.3-8.0 (17H, m, aromatic protons included 3 exchanged with D_2O, NH_2 and pyrazolone proton).

N.m.r. spectrum ($CDCl_3$): δ3.63 (2H, s, CH_2); 6.4-8.2 (14H, m, aromatic protons); 5.0-5.6 (3H, br., exchanged with D_2O, NH_2 and pyrazolone proton).

Mass spectrum: See Fig. 1.

Accurate mass measurements: 248.0945, $C_{16}H_{12}N_2O$ requires 248.0950; 106.0661, C_7H_8N requires 106.0657; 93.0584, C_6H_7N requires 93.0579.

Method C: Reduction with sodium borohydride and palladium-charcoal in methanol.

The title compound (2.0 g) in methanol (100 ml) was reduced as described in the general procedure (p. 245). When the reaction mixture was acidified with glacial acetic acid, some yellow crystals (0.08 g), m.p. 176-8° separated. This was found to be the spiro(N-hydroxyindoline) pyrazolone (342). The filtrate was concentrated to half the original volume. When cooled, it yielded a pale-yellow solid which was recrystallized as off-white crystals from ethanol (0.56 g), m.p. 148-51° identified (i.r.) as 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b).

Reductions of 4-(5-chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (318c).

Method A: Reduction with sodium borohydride in dioxane.

The title compound (3.0 g) was reduced according to the method described for the reduction of the analogs (318b, c) (Method A). Crystallization of the resulting precipitate (2.65 g) from ethanol gave 4-(5-chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (319c) as a pale-yellow solid, m.p. 145-6°.

I.r. spectrum (nujol): 2100-3300 br. (OH); 1526 and 1342 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ 2.12 (3H, s, CH_3); 4.03 (2H, s, CH_2); 7.1-8.3 (8H, m, aromatic protons); 11.0-12.7 (1H, br. s, exchanged with D_2O,OH).

Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.39; H, 4.10; N, 12.22.

Found: C, 59.53; H, 4.21; N, 12.47.

Method B: Reduction with sodium borohydride and palladium charcoal in dioxane.

The title compound (2.0 g) in dioxane (50 ml) was reduced according to the general procedure (p. 245). The filtrate, on acidification with dilute acetic acid and dilution with water, yielded a white precipitate (1.3 g). Crystallization from ethanol gave spiro[(5-chloro-

1-hydroxyindoline)-2,4'(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one) (347) as a white solid, m.p. 143-5° which reduced Tollen's reagent and gave a positive reaction with triphenyltetrazolium chloride.

I.r. spectrum (nujol): 1685 (C=O); 3280, br. (N–OH); 1605 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.2 (3H, s, CH_3); 3.46 (2H, s, CH_2);
6.9-8.1 (8H, m, aromatic protons); 8.6 (1H, br., exchanged
with D_2O, N–OH).

Mass spectrum: See Fig. 25.

Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30; N, 12.82.
Found: C, 62.13; H, 4.48; N, 13.09.

The mother liquors, on concentration gave small amounts (0.18 g) of white crystals melted at 118-20° which was identified as 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazoline-5-one (321c).

I.r. spectrum (nujol): 1630 (bonded C=O); 1602 (C=N), 2100-3420,
br. with maxima at 3230 and 3390 (OH and NH_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.08 (3H, s, CH_3); 3.48 (2H, s, CH_2);
6.4-8.0 (11H, m, aromatic protons included 3 exchanged with
D_2O).

Anal. Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.06; H, 5.14; N, 13.39.
Found: C, 65.12; H, 5.21; N, 13.45.

Method C: Reduction with sodium borohydride and palladium-charcoal in methanol.

The general procedure described on p. 245 was used for the catalytic (Pd-C) sodium borohydride reduction of the title compound (2.0 g) in methanol (120 ml). The filtered reaction mixture was acidified with glacial acetic acid then concentrated (50 ml). When cooled, 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321c) separated as pale-yellow solid (1.1 g), m.p. 110-3°. Recrystallization twice from ethanol raised the m.p. to 119-20°.

Reductions of 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (319a).

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution.

Following the general procedure outlined on p. 245, a solution of the title compound (4.0 g) in 10% aqueous sodium hydroxide (80 ml) was reduced with sodium borohydride and palladium-charcoal. The filtered reaction mixture was acidified with ice-cold dilute acetic acid to give a copious white precipitate. This was crystallized from ethanol to white needles (3.4 g), m.p. 153-4°. The i.r. and n.m.r. spectra of this product were identical to those of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a).

When the filtrate was acidified with dilute hydrochloric acid, it yielded a pale-yellow precipitate. Crystallization from methanol gave 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a) hydrochloride, m.p. 253-4°. The same compound was obtained quantitatively as white crystals, m.p. 255-6° when dry hydrogen chloride was bubbled through a solution of (321a) in tetrahydrofuran.

I.r. spectrum (nujol): 1900-3280, broad with low intensity maxima at 2080, 2630 and 3090 cm^{-1}

Anal. Calcd. for $C_{17}H_{18}ClN_3O$: C, 64.65; H, 5.74; N, 13.31.

Found: C, 64.71; H, 5.72; N, 13.19.

Method B: Reduction with iron and ferrous ammonium sulfate.

Reduced iron (2.0 g) was added to a solution of the title compound (1.0 g) in ethanol (60 ml) and the mixture was heated to boiling. An aqueous solution (25 ml) of ferrous ammonium sulfate (0.6 g) was added to the mixture and heating was continued for two hours. The filtered reaction mixture was evaporated to dryness, and the dried residue was heated with absolute ethanol (15 ml) and filtered. The filtrate, on evaporation, yielded an off-white solid (0.62 g), m.p. 148-52°. This was recrystallized from ethanol to give a colorless solid, m.p. 181-2°, the infrared spectrum of which indicated that it was spiro[(1-hydroxyindoline)-2,41-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (338).

When this reaction was repeated, the results were not consistent. It sometimes gave the above compound but on other occasions it yielded the 4-(2-aminobenzyl) pyrazolone (321a) or a mixture of both products. When a mixture was obtained, it was dissolved in 10% sodium hydroxide then extracted with ether. Evaporation of the dried ether extract yielded the spiro (N-hydroxyindoline) pyrazolone (338). Acidification of the aqueous layer with acetic acid gave the 4-(2-aminobenzyl)pyrazolone (321a).

Method C: Reduction with zinc and ammonium chloride.

Ammonium chloride (0.2 g) in water (10 ml) was added to a solution of 3-methyl-4-(2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (1.0 g) in dilute (50%) ethanol (40 ml). Zinc dust (0.5 g) was added and the mixture was refluxed for two hours under nitrogen. The filtered reaction mixture was dried under vacuum, dissolved in absolute ethanol and refiltered. Concentration of the filtrate yielded white crystals m.p. 125-6°. Recrystallization from ethanol raised the m.p. to 128-9°. This compound was identified (i.r. and mixed m.p.) as the spiro(indoline)pyrazolone (339) described earlier (p. 248).

Method D: Reduction with zinc and acetic acid.

Zinc dust (1.0 g) was added in small quantities to a stirred solution of the title compound (2.0 g) in boiling glacial acetic acid (20 ml). The mixture was heated under reflux for six hours then filtered and the filtrate was diluted with water (100 ml). The yellow flocculant precipitate formed was collected and crystallized from aqueous ethanol as yellow solid, m.p. 166-8° identified as 3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (376a). Reported (Brack, 1962) m.p. 178°.

I.r. spectrum (nujol): 1618 (C=N) cm^{-1}; no NH or OH bands.

N.m.r. spectrum ($CDCl_3$): δ 2.78 (3H, s, CH_3); 7.3-9 (10H, m, aromatic protons).

Mass spectrum: 259 (M^+, 100%), 258 (27%), 244 (33%), 218 (21%).

Anal. Calcd. for $C_{17}H_{13}N_3$: N, 16.21.

Found: N, 15.38.

The same compound was obtained in low yield (0.15 g), when 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) was heated under reflux in acetic acid (10 ml) for three hours. Evaporation of acetic acid gave a yellow oil which crystallized from ethanol into dark yellow crystals, m.p. 158-61°.

Method E: Catalytic hydrogenation.

(i) A solution of 3-methyl-4-(2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (1.0 g) in absolute ethanol (150 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of a catalytic amount (~30 mg) of platinum oxide. After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the solvent evaporated, leaving a solid residue (0.58 g) which was crystallized from ethanol to colorless crystals m.p. 153-4°. Infrared and n.m.r. spectra of this product were identical with those of the 4-(2-aminobenzyl)pyrazolone (321a).

(ii) The above reduction was repeated and the reaction mixture was set aside for 24 hours then filtered. Evaporation of the solvent yielded a colorless solid, the i.r. spectrum of which showed absorption bands at 1690 (C=O) and a broad band between 2100 and 3500 with maxima at 3200, 3340 and 3400 cm^{-1}. This product was treated with dilute sodium hydroxide solution and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated. The solid residue formed (0.8 g) crystallized from ethanol into colorless crystals (0.32 g), m.p. 146-9° identified as spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline)] (337a).

I.r. spectrum (nujol): 1690 (C=O); 3405 (N—H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ1.06 (3H, d, J=6.5 Hz, CH_3); 1.93 (3H, s, CH_3); 3.01 (2H, doublet of doublets, J=16.5 Hz, CH_2); 3.7 (1H, s, CH); 3.86 (1H, br. s, exchanged with D_2O, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: See Fig. 6.

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.72; H, 6.27; N, 13.76.

Found: C, 74.61; H, 6.04; N, 13.67.

Acidification of the sodium hydroxide solution with dilute acetic acid gave a white flocculant precipitate (0.3 g) which was crystallized from ethanol to yield 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a) as a colorless solid, m.p. 151-2°.

(iii) The previous reaction was repeated in propanol (150 ml). Crystallization of the alkali-soluble product gave 0.26g of the 4-(2-aminobenzyl)pyrazolone (321a), m.p. 150-2°. The ethereal extract was evaporated and crystallized from ethanol yielding a colorless solid (0.44 g), m.p. 141-3° identified as spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (337b).

I.r. spectrum (nujol): 1690 (C=O), 3390 (N–H) $\mathrm{cm^{-1}}$.

N.m.r. spectrum ($CDCl_3$): δ1.0-1.8 (5H, m, CH_2CH_3); 1.88 (3H, s, CH_3); 3.05 (2H, doublet of doublets, J=16.5 Hz, CH_2); 3.5 (1H, s, CH); 4.05 (1H, br. s, exchanged with D_2O, N H); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: 319 (M^+, 100%), 302 (2%), 290 (62%), 146 (90%).

Anal. Calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16.
Found: C, 75.40; H, 6.71; N, 12.98.

(iv) When the same reduction was performed in methanol (150 ml), it yielded a solid product which crystallized from methanol into colorless crystals (0.28 g), m.p. 153-4°. This was identified as spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(1',2',3',4'-tetrahydroquinoline)] (383a).

I.r. spectrum (nujol): 1690 (C=O), 3425 (N–H) $\mathrm{cm^{-1}}$.

N.m.r. spectrum ($CDCl_3$): δ2.01 (3H, s, CH_3); 3.0 (2H, doublet of doublets, J=17.5 Hz, CH_2); 3.91 (1H, br. s, exchanged with D_2O, NH); 6.6-8.3 (9H, m, aromatic protons).

Mass spectrum: See Fig. 6.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42.

Found: C, 73.87; H, 6.01; N, 13.98.

No other products was isolated from this reaction.

Reductions of 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (319b).

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution.

The title compound (2.0 g) was reduced according to the general procedure (p. 245). Acidification of the filtrate with dilute acetic acid gave a white flocculant precipitate which crystallized from ethanol into colorless crystals (1.8 g), m.p. 151-3°. This was 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b). When the filtrate was acidified with dilute hydrochloric acid, it precipitated an off-white product. Crystallization from methanol yielded 321b hydrochloride as a white solid, m.p. 211-3°. Reported (Coutts and Edwards, 1966) m.p. 182-3°.

I.r. spectrum (nujol): 1900-3200, broad with low intensity maxima at 1985, 2060, 2635 and 3080 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}ClN_3O$: C, 64.65; H, 5.74; N, 13.31.

Found: C, 64.71; H, 5.59; N, 13.26.

Method B: Reduction with iron and ferrous ammonium sulfate.

A solution of the title compound (1.0 g) in ethanol (80 ml) was reduced with reduced iron and ferrous ammonium sulfate as described for the reduction of the methyl pyrazolone (319a) (Method B). The resulting white solid (0.65 g) was crystallized from ethanol as colorless crystals, m.p. 152-3°. The i.r. spectrum of this compound was identical with that of the amine (321b) prepared as described above.

Method C: Reduction with zinc and ammonium chloride.

The title compound (1.0 g) was reduced as described for the reduction of 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (319a) to yield pale-yellow crystals (0.78 g), m.p. 193-4°. This was identified as spiro[(indoline)-2,4'-(1',3'-diphenyl-1*H*-pyrazolin-5'-one)] (343).

I.r. spectrum (nujol): 1728 (C=O); 3390 (N–H) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ3.5 (2H, br. s, CH_2); 4.6 (1H, br. s, exchanged with D_2O, NH); 6.6-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 21.

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.85; H, 5.05; N, 12.38.

Found: C, 77.69; H, 5.14; N, 12.41.

Method D: Reduction with zinc and acetic acid.

1,3-Diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (2.0 g) was reduced with zinc dust (1.0 g) and acetic acid (20 ml) according to method D described for the reduction of the methyl analog (319a). When the reaction mixture was filtered, a dark yellow solid (0.8 g), m.p. 158-60° crystallized from the filtrate. This was collected and recrystallized from ethanol to yield golden yellow needles, m.p. 162-3°, 1,3-diphenyl-1*H*-pyrazolo[3,4-b]quinoline (376b). A further crop (0.5 g), m.p. 157-8° was obtained from the filtrate by dilution with water (100 ml).

I.r. spectrum (nujol): 1618 (C=N) cm^{-1}; No NH or OH bands.

N.m.r. spectrum ($CDCl_3$): δ7.0-8.9 (15H, m, aromatic protons).

Mass spectrum: 321(M^+, 100%), 320 (30%), 244 (11%), 218 (9%).

Anal. Calcd. for $C_{22}H_{15}N_3$: C, 81.22; H, 4.71; N, 13.08.

Found: C, 81.43; H, 4.81; N, 13.41.

The same compound was obtained by heating a solution of the 4-(2-aminobenzyl)pyrazolone (321b, 0.5 g) in acetic acid (10 ml) for two hours. When the solution was cooled, the pyrazoloquinoline (376b) separated as yellow crystals (0.35 g), m.p. 158-9°.

Method E: Catalytic hydrogenation.

(i) The title compound (1.0 g) in methanol (200 ml) was hydrogenated over platinum oxide (~30 mg) at room temperature and atmospheric pressure. When the calculated amount of hydrogen was taken up, the catalyst was filtered off and the solvent evaporated to give a yellow solid. Crystallization from methanol yielded pale-yellow crystals (0.35 g), m.p. 188-9°. This was identified as spiro-[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(1',2',3',4'-tetrahydroquinoline)] (377a)*.

I.r. spectrum (nujol): 1700 (C=O); 3365 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ3.34 (2H, s, CH_2); 3.57 (2H, br. s, CH_2); 3.95 (1H, br. s, NH); 6.5-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 7.

Accurate mass measurements: 118.0653, C_8H_8N requires 118.0657.

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89.

Found: C, 77.99; H, 5.496; N, 11.27.

The above reduction was repeated in the solvents described yielding the following compounds:

Spiro[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline] (377b) was obtained as off-white needles (0.75 g, m.p. 165-6°) when ethanol (200 ml) was used as solvent.

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* The same product was obtained when the reaction was catalyzed with palladium-charcoal.

I.r. spectrum (nujol): 1712 (C=O); 3405 (N H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ1.15 (3H, d, J=6.5 Hz, CH_3); 3.5 (2H, doublet of doublets, J=17 Hz, CH_2); 3.6 (1H, q, CH); 3.63 (1H, br. s, exchanged with D_2O, NH); 6.4-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 7.

Accurate mass measurements: 367.1680, $C_{24}H_{21}N_3O$ requires 367.1685; 352.1450, $C_{23}H_{18}N_3O$ requires 352.1450; 132.0813, $G_{19}H_{10}N$ requires 132.0813.

Anal. Calcd. for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.43.

Found: C, 78.47; H, 5.60; N, 11.60.

<u>Spiro[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (377c)</u> was isolated as colorless crystals (0.59 g, m.p. 159-60°) when a solution of 1.0 g of (319b) in propanol (200 ml) was hydrogenated over platinum oxide.

I.r. spectrum (nujol): 1710 (C=O); 3415 (N-H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ0.9-1.5 (5H, m, J=6.5 Hz, CH_2CH_3); 3.35 (2H, doublet of doublets, J=17.5 Hz, CH_2); 3.64 (1H, br. s, exchanged with D_2O, NH); 6.3-8.3 (14H, m, aromatic protons).

Mass spectrum: 381 (M^+, 100%), 364 (2%), 352 (42%), 352 (42%), 146 (78%).

Accurate mass measurements: 381.1837, $C_{25}H_{23}N_3O$ requires 381.1841; 146.0966, $C_{10}H_{12}N$ requires 146.0970.

Anal. Calcd. for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.07; N, 11.02.

Found: C, 78.63; H, 6.04; N, 11.07.

<u>Spiro[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-phenyl-1',2',3',4'-tetrahydroquinoline)] (377d)</u> was obtained as pale-yellow solid (0.28 g,

m.p. 207-9°) when the above reduction was repeated in benzyl alcohol (200 ml).

I.r. spectrum (nujol): 1698 (C=O); 3380 (N—H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ3.45 (2H, doublet of doublets, J=17 Hz, CH_2); 4.68 (1H, s, CH); 4.07 (1H br., exchanged with D_2O, NH); 7-7.8 (19H, m, aromatic protons).

Mass spectrum: 429 (M^+, 100%), 412 (2%), 352 (3%), 194 (67%), 193 (25%).

Anal. Calcd. for $C_{29}H_{23}N_3O$: C, 81.07; H, 5.39; N, 9.78.

Found: C, 81.12; H, 5.43; N, 9.80.

4-(2-Aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b) was isolated as colorless crystals (0.78 g, m.p. 151-2°) when a solution of 1.0 g of (319b) in dioxane (100 ml) was hydrogenated over platinum oxide.

Reductions of 4-(5-chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (319c).

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution.

A solution of the title compound (2.0 g) in 10% aqueous hydroxide (40 ml) was reduced according to the general procedure (p. 245). The filtrate was acidified with dilute acetic acid to give a white precipitate which crystallized from ethanol as a colorless solid (1.2 g), m.p. 119-21°. The i.r. and n.m.r. spectra were identical with those of 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321c). When this compound was dissolved in aqueous sodium hydroxide, and the alkaline solution acidified with dilute hydrochloric acid, 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-

pyrazolin-5-one (321c) hydrochloride precipitated quantitatively as a pale-yellow solid, m.p. 229-30°.

I.r. spectrum(nujol): 1900-3250, broad with low intensity maxima at 2075, 2635 and 3090 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}Cl_2N_3O$: C, 58.29; H, 4.89; N, 11.99.

Found: C, 58.53; H, 5.03; N, 12.21.

Method B: Reduction with zinc and ammonium chloride.

The title compound (1.0 g) was reduced as described for the reduction of (319a) (Method C). After removal of the excess zinc and zinc oxide, the solution was evaporated. Crystallization of the dried residue from ethanol gave a white crystalline solid (0.4 g), m.p. 153-4°. This was identified as spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346a).

I.r. spectrum (nujol): 1710 (C=O); 3365 (N—H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.04 (3H, s, CH_3); 3.33 (2H, doublet of doublets, J=16 Hz, CH_2); 4.0 (1H, br. s, exchanged with D_2O, N—H); 6.4-8.1 (8H, m, aromatic protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48.

Found: C, 65.06; H, 4.67; N, 13.21.

Concentration of the mother liquor remaining after the removal of the above product yielded a second crystalline powder (0.15 g), m.p. 144-5° the i.r. spectrum of which was found to be identical with that of spiro[(5-chloro-1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (347).

Reactions of 4-(2-Aminobenzyl)-2-pyrazolin-5-ones (321a, b)

(1) Reactions with dimethylsulfate

a. To an ice-cold solution of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) in 10% sodium hydroxide (15 ml), dimethylsulfate (0.25 g) was added dropwise with stirring. The mixture was heated under reflux for one hour. After cooling, the gummy precipitate formed was collected and washed with 10% sodium hydroxide then with water. Crystallization from methanol gave colorless needles (0.18 g), m.p. 191-2°. The product identified as 4-(2-aminobenzyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (324a).

I.r. spectrum (nujol): 1624 (bonded C=O); 3230 and 3375 (NH_2) cm^{-1}.

N.m.r. spectrum ($DMSO-d_6$): $\delta 2.2$ (3H, s, $C-CH_3$); 2.98 (3H, s, $N-CH_3$); 3.35 (2H, s, CH_2); 5.16 (2H, br. s, exchanged with D_2O, NH_2); 6.3-7.6 (9H, m, aromatic protons).

Mass spectrum: 293 (M^+, 100%), 263 (61%), 56 (97%).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32.

Found: C, 73.78; H, 6.43; N, 14.12.

b. 4-(2-Aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) was treated with dimethyl sulfate in a similar manner to yield 4-(2-aminobenzyl)-3-methyl-1,3-diphenyl-3-pyrazolin-5-one (324b) as colorless needles (0.25 g), m.p. 195-6°.

I.r. spectrum (nujol): 1630 (bonded C=O); 3235 and 3405 (NH_2) cm^{-1}.

N.m.r. spectrum ($DMSO-d_6$): $\delta 2.9$ (3H, s, $N-CH_3$); 3.44 (2H, s, CH_2); 5.17 (2H, br. s, exchanged with D_2O, NH_2); 6.3 7.9 (14H, m, aromatic protons).

Mass spectrum: 355 (M^+, 72%), 325 (40%), 118 (100%).

Accurate mass measurements: 325.1337, $C_{22}H_{17}N_2O$ requires

325.1341, 118.0658, C_8H_8N requires 118.0657.

Anal. Calcd. for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82.

Found: C, 77.40; H, 5.97; N, 12.11.

(2) Reactions with acetic anhydride

a. A solution of 4-(2-aminobenzyl) 3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) in acetic anhydride (5.0 ml) was heated under reflux for one hour. The cooled solution was poured into 5% aqueous sodium hydroxide and stirred until homogeneous; then the alkaline solution was extracted with ether. This was dried (Na_2SO_4) and evaporated to give a yellow solid residue which crystallized from ethanol into white crystals (0.4 g), m.p. 208-9° identified as 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).

I.r. spectrum (nujol): 1660 (C=O); 2500-3300 br. with maximum at 3180 (OH and NH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.14 (3H, s, CH_3); 2.20 (3H, s, CH_3); 3.57 (2H, s, CH_2); 7.0-7.9 (9H, m, aromatic protons); 9.2 (1H, br. s, exchanged with D_2O, NH).

Mass spectrum: See Fig. 2.

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08.

Found: C, 70.87; H, 5.81; N, 13.12.

b. When the above reaction was repeated and the mixture heated under reflux for three hours, a colorless crystalline product (0.43 g), m.p. 113-4° was obtained from ethanol. This was 5-acetyloxy-4-(2-diacetylaminobenzyl)-3-methyl-1-phenylpyrazole (326a).

I.r. spectrum (nujol): 1790 (ester C=O); 1730 and 1685 (diacetyl C=O); 1600 (C=N) cm^{-1}

N.m.r. spectrum (DMSO-d_6): δ2.02 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.11 (6H, s, diacetyl protons); 3.48 (2H, s, CH_2); 7.2-7.5 (9H, m, aromatic protons).

Mass spectrum: See Fig. 3.

Anal. Calcd. for $C_{23}H_{23}N_3O_4$: C, 68.15; H, 5.68; N, 10.37.

Found: C, 68.03; H, 5.71; N, 10.51.

This compound was insoluble in aqueous sodium hydroxide, but on stirring for several hours in 5% sodium hydroxide solution it dissolved. The solution was filtered and acidified with acetic acid to give a white precipitate which crystallized from ethanol, m.p. 208-10°. The i.r. spectrum of this product was identical with that of the monoacetyl derivative (332a).

c. Similarly, heating 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) in acetic anhydride (5.0 ml) for one hour yielded 4-(2-acetylaminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (332b) as white crystals (0.41 g) m.p. 219-21° (ethanol).

I.r. spectrum (nujol): 1662 (C=O); 2100-3260 br. (NH and OH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.1 (3H, s, CH_3); 3.84 (2H, s, CH_2); 6.8-8.0 (15H, m, aromatic protons); 9.33 (1H, br. s, exchanged with D_2O, NH).

Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.21; H, 5.52; N, 10.96.

Found: C, 75.22; H, 5.53; N, 10.75.

d. A triacetyl derivative, 5-acetyloxy-4-(2-diacetylaminobenzyl)-1,3-diphenylpyrazole (326b) was isolated as white crystals (0.4 g), m.p. 110-11° (from ethanol) when the above reaction was repeated and heating with acetic anhydride was prolonged for four hours.

I.r. spectrum (nujol): 1793 (ester C=O); 1718 and 1705 (diacetyl C=O); 1595 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.02 (6H, s, diacetyl protons); 2.2

(3H, s, $OCOCH_3$); 3.75 (2H, s, CH_2); 7.05-7.7 (14H, m, aromatic protons).

Anal. Calcd. for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.98.

Found: C, 72.13; H, 5.18; N, 8.85.

Hydrolysis of this compound with 5% aqueous sodium hydroxide readily gave the monoacetyl derivative (332b).

(3) Reaction with benzoyl chloride

To an ice-cold solution of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) in dilute sodium hydroxide (10 ml) was added benzoyl chloride (0.75 ml) with vigorous stirring. After one hour, more benzoyl chloride (0.5 ml) was added and stirring continued at room temperature for a further 30 minutes. The reaction mixture was extracted with ether then the ethereal extract was washed successively with 10% hydrochloric acid, 10% sodium carbonate and water. Concentration of the dried ethereal solution gave white shiny crystals (0.51 g), m.p. 137-8^o identified as 4-(2-benzoylamino)-5-benzoyloxy-3-methyl-1-phenylpyrazole (325).

I.r. spectrum (nujol): 1760 (OCOPh); 1645 (NHCOPh); 1600 (C=N), 3315 (N—H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.12 (3H, s, CH_3); 3.8 (2H, s, CH_2); 8.0 (-H, br. s, exchanged with D_2O, NH); 6.8-7.9 (19H, m, aromatic protons).

Mass spectrum: 487 (M^+, 4%), 382 (3%), 366 (9%), 365 (30%), 105 (100%).

Anal. Calcd. for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.61.

Found: C, 76.43; H, 5.33; N, 8.60.

(4) Attempted preparation of 5-acetyloxy-4-(2-aminobenzyl)-1-phenylpyrazoles (335a, b).

a. A solution of 3-methyl 4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (1.0 g) in acetic anhydride (10 ml) was heated under reflux for one hour. After cooling, the reaction mixture was poured into ice-cold 5% sodium hydroxide solution (100 ml). Stirring precipitated a pale-yellow solid (1.05 g) which crystallized from ethanol yielding 5-acetyloxy-3-methyl-4-(2-nitrobenzyl)-1-phenylpyrazole (334a) as white crystals, m.p. 85-6°.

I.r. spectrum (nujol): 1781 (C=O); 1600 (C=N) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.17 (3H, s, C—CH_3); 2.03 (3H, s, (CO—CH_3); 4.05 (2H, s, CH_2); 7.2-8.1 (9H, m, aromatic protons).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.94; H, 4.88; N, 11.95.
Found: C, 64.77; H, 5.15; N, 11.79.

b. Acetylation of 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (1.0 g) using the above method yielded 5-acetyloxy-1,3-diphenyl-4-(2-nitrobenzyl)pyrazole (334b) (1.01 g) as a pale-yellow crystalline powder, m.p. 118-9° (ethanol).

I.r. spectrum (nujol): 1790 (C=O); 1597 (C=N) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.02 (3H, s, CO CH_3); 4.28 (2H, s, CH_2); 7.2-8.1 (14H, m, aromatic protons).

Mass spectrum: 413 (M^+, 12%), 371 (51%), 354 (14%), 353 (18%).

Anal. Calcd. for $C_{24}H_{19}N_3O_4$: C, 69.70; H, 4.64; N, 10.16.
Found: C, 69.90; H, 5.06; N, 10.41.

c. 5-Acetyloxy-2-methyl-4-(2-nitrobenzyl)-1-phenylpyrazole (0.5 g) in ethanol (20 ml) was hydrogenated over platinum oxide at room temperature and atmospheric pressure. When the calculated amount of hydrogen was taken up, the catalyst was filtered and the solvent evaporated to yield a yellow oil. Trituration of this oil with methanol gave a pale-yellow solid (0.15 g). This was crystallized as pale-yellow crystals, m.p. 205-7°, from the same solvent and was found (i.r., mixed m.p.) to be identical to the previously identified 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).

d. The above product (332a) was also obtained when a solution of 5-acetyloxy-2-methyl-4-(2-nitrobenzyl)-1-phenylpyrazole (0.5 g) in dioxane (20 ml) was reduced with sodium borohydride and palladium-charcoal. The general procedure outlined on p. 245 was followed. After acidification of the filtered reaction mixture with acetic acid, it was extracted with ether. The ethereal extract was washed with 10% sodium carbonate, dried (Na_2SO_4), and then evaporated. Crystallization of the resulting semi-solid from ethanol yielded a pale-yellow solid (0.12 g), m.p. 206-7° identified (i.r., mixed m.p.) as the 4-(2-acetylaminobenzyl)pyrazolone (332a).

e. Hydrogenation of 5-acetyloxy-1,3-diphenyl-4-(2-nitrobenzyl)pyrazole (0.5 g) over platinum oxide as described above gave a white crystalline compound (0.21 g), m.p. 218-9° (ethanol). Comparison of its i.r. and n.m.r. spectra with those of an authentic sample indicated that it was 4-(2-acetylaminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (332b).

Reactions of spiro (1-hydroxyindoline)-2,4'-(1'-phenyl-1*H*-pyrazolin-5'-ones)

(1) Reduction:

Method A: (i) A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-

methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (338, 0.5 g) in ethanol (70 ml) was hydrogenated over platinum oxide with hydrogen at atmospheric pressure and room temperature. After the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*, then cooled, and a white crystalline product (0.43 g) separated. This was recrystallized from ethanol giving spiro[(indoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (339) as white crystals, m.p. 129-30°.

(ii) Spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1*H*-pyrazolin-5'-one)] (342, 0.5 g) was hydrogenated in a similar manner to yield the corresponding indoline (343) as a pale-yellow solid (0.38 g) m.p. 192-4°.

(iii) Similarly, spiro[(5-chloro-1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (347, 0.35 g) was reduced by catalytic hydrogenation over platinum oxide giving the previously identified spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazoline-5'-one)] (346a) as colorless crystals (0.21 g), m.p. 152-3°.

Method B: (i) To a heated solution of the spiro(N-hydroxyindoline)-pyrazolone (338, 0.5 g) in 30 ml ethanol was added 1.0 g of reduced iron followed by a solution of ferrous ammonium sulfate (0.3 g) in water (25 ml) and the mixture was heated, under reflux, for ten hours then filtered. The filtrate was evaporated to dryness and the residue was dissolved in hot ethanol and refiltered. Cooling of this filtrate yielded the spiro(indoline)pyrazolone (339) as white crystals (0.44 g), m.p. 128-9°.

(ii) Reduction of spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1*H*-pyrazolin-5'-one)] (0.4 g) as described above yielded pale yellow crystals (0.29 g) m.p. 192-4° which was identified (i.r.) as spiro[(indoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (343).

Method C: Ammonium chloride (0.1 g) in water (5 ml) was added to a stirred solution of spiro (1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one) (0.5 g) in 60% ethanol (25 ml). Zinc powder (0.5 g) was added in small portions and the mixture was refluxed for an hour. After removal of the excess zinc and zinc oxide, the solution was concentrated in vacuo and extracted with chloroform (50 ml). Evaporation of the dried ($CaCl_2$) chloroform gave a white solid (0.41 g) which crystallized from ethanol as colorless crystals, m.p. 127-9° identified (i.r.) as the spiro(indoline)pyrazolone (339).

(2) Oxidation:

A) Air was bubbled into a solution of the spiro(N-hydroxyindoline)pyrazolone (338, 0.3 g) in 60% ethanol (15 ml) at room temperature for two hours. After being allowed to stand overnight, the solution was evaporated and starting material was recovered. Similar results were obtained when the reaction was repeated in tetrahydrofuran.

B) Air was bubbled for three hours through a solution of the spiro(1-hydroxyindoline)pyrazolone (338, 0.3 g) in aqueous (60%) ethanol (25 ml) containing ammonia (1 ml) and copper sulfate (5 mg). Water (50 ml) was added and the dark-brown precipitate which formed was extracted into chloroform (20 ml). The dried ($CaCl_2$) chloroform solution was concentrated in vacuo and the residue was crystallized from aqueous ethanol as a dark-brown solid (0.18 g), m.p. 121-4°. No satisfactory analysis could be obtained for this product, but its mass spectrum had a strong molecular ion at m/e 291 ($C_{17}H_{13}N_3O_3$).

This compound was tentatively identified as spiro[(2H-indolenine 1-oxide)-2,4'-(3'-methyl-1'-phenyl-2'-pyrazolin-5'-one)].

I.r. spectrum (nujol): 1728 (C=O) cm^{-1}, no NH or OH absorption.

N.m.r. spectrum ($CDCl_3$): δ2.07 (3H, s, CH_3); 6.7-8.2 (10H, m, aromatic protons).

(3) Attempted dehydration:

a) Concentrated sulfuric acid (0.5 ml) was added dropwise to a suspension of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in methanol (15 ml). The mixture was heated under reflux for two hours, then left overnight at room temperature. The solution was made alkaline with dilute sodium hydroxide then reacidified with glacial acetic acid and extracted with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated to dryness to give a dark-brown oil. When triturated with methanol, this oil gave a dark-yellow solid which was crystallized from the same solvent into brown crystals (0.29 g), m.p. 170-2°.

I.r. spectrum (nujol): 1635 (C=O); 3305 (NH or OH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.62 (3H, s, CH_3); 3.89 (3H, s, OCH_3); 6.8-7.7 (6 or 7H, m, aromatic protons); 9.4 (1H, br. s, exchanged with D_2O, NH or OH?).

Mass spectrum: 189 (M^+, 100%), 174 (92%), 146 (39%), 131 (9%), 119 (16%), 43 (16%).

Anal. Found (Average): C, 68.76; H, 5.31; N, 8.20.

This compound was not identified.

b) When the above reaction was repeated at 0°, it gave a dark-green oil which solidified when triturated with methanol. This was crystallized from ethanol as white crystals (0.37 g), m.p. 135-7°

identified as spiro[(5-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346b).

I.r. spectrum (nujol): 1710 (C=O); 3310 (N–H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.03 (3H, s, C–CH_3); 3.77 (3H, s, O–CH_3); 3.33 (2H, doublet of doublets, J=16.5 Hz, CH_2); 4.28 (1H, br. s, exchanged with D_2O, NH); 6.5-8.4 (8H, m, aromatic protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67.
Found: C, 70.21; H, 5.49; N, 13.70.

c) Spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) was dissolved in an ice-cold mixture of dioxane (8 ml) and water (7 ml). Concentrated sulfuric acid (0.5 ml) was added dropwise and the reaction mixture was allowed to stand at room temperature for 12 hours. Dilute sodium hydroxide (10 ml) was added, and the solution was reacidified with glacial acetic acid and extracted with chloroform. Evaporation of the dried chloroform extract yielded a pale-brown solid which crystallized from aqueous ethanol into an off-white solid (0.19 g), m.p. 114-16°. Recrystallization of this alkali-soluble product from ethanol did not raise its melting point. This compound was identified as spiro[(5-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346c).

I.r. spectrum (nujol): 3100-3500 br. (NH and OH); 1709 (C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.1 (3H, s, CH_3); 3.29 (2H, br. s, CH_2); 4.7 (1H, br. s, exchanged with D_2O, NH); 11.1 (1H, br. s, exchanged with D_2O, OH); 6.7-8.3 (8H, m, aromatic protons).

Mass spectrum: 293 (M^+, 19%), 265 (26%).

This compound analyzed indifferently for $C_{17}H_{15}N_3O_2$.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.16.

Found: C, 70.99; H, 4.53.

(4) Reactions with nucleophiles:

a. Reaction with hydrogen chloride

A stream of hydrogen chloride was passed through a solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in tetrahydrofuran (10 ml) for 30 seconds at 0°. The solution was left standing at 0° for 12 hours then evaporated in vacuo to dryness. The resulting black semi-solid was chromatographed on a silica gel column using petroleum ether (30-60°, 100 ml) then benzene (100 ml) as solvent. Evaporation of the benzene eluate gave a dark-yellow solid which crystallized from ethanol yielding spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one] (346a) as white crystals (0.26 g), m.p. 153-4°.

b. Reaction with acetic acid

A solution of the spiro(1-hydroxyindoline)pyrazolone (338, 0.5 g) in glacial acetic acid (10 ml) was heated under reflux for one hour. The resulting red solution was added to cold water (100 ml) and the buff precipitate formed was extracted with ether. The ethereal extract was washed with a saturated solution of sodium bicarbonate then with water and dried (Na_2SO_4). Evaporation of this extract yielded a pale-yellow solid (0.38 g) which crystallized from ethanol into off-white crystals, m.p. 120-1°. This was spiro[(5-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346d).

I.r. spectrum (nujol): 1712 (lactam C=O); 1744 (ester C=O); 3380 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.06 (3H, s, C-CH_3); 2.23 (3H, s, $OCOCH_3$); 3.36 (2H, doublet of doublets, J=15 Hz, CH_2); 4.5 (1H, br. s, exchanged with D_2O, NH); 6.5-8.5 (8H, m, aromatic protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53.

Found: C, 67.95; H, 5.17; N, 12.31.

(5) Acylation and sulfonation reactions:

a. Reactions with acetic anhydride

(i) A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (0.6 g) in acetic anhydride (10 ml) was heated under reflux for one hour. The cooled solution was poured into ice-cold 5% aqueous sodium hydroxide and stirred until homogeneous. The precipitate was collected and crystallized from ethanol to yield a pale-yellow solid (0.27 g), m.p. 306-8° (compound A).

I.r. spectrum (nujol): 1625 and 1640 (C=O); 3410 (NH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.63 (3H, s, CH_3); 4.0-5.1 (1H, br. s, exchanged with D_2O, NH); 7.2-8.3 (9H, m, aromatic protons).

Mass spectrum: See Fig. 4.

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.24; H, 4.76; N, 15.28.

Found: C, 74.49; H, 4.57; N, 14.98.

The mother liquor remaining after the removal of the above product was evaporated. The resulting reddish solid was crystallized twice from benzene/petroleum ether (40-60°) yielding spiro[(1,5-diacetoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-

pyrazolin-5'-one)] (363) as off-white crystals (0.13 g), m.p. 137-9°.

I.r. spectrum (nujol): 1667 (cyclic amide C=O); 1715 (lactam C=O); 1760 (ester C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (DMSO-d_6): δ2.02 (3H, s, $C-CH_3$); 2.3 (3H, s, $OCOCH_3$); 2.50 (3H, s, $NCOCH_3$); 3.43 (2H, br. s, CH_2); 7.0-8.3 (8H, m, aromatic protons).

Mass spectrum: 377 (M^+, 30%), 335 (31%), 293 (100%), 276 (19%), 275 (53%), 274 (34%), 265 (21%).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13.

Found: C, 66.71; H, 5.12; N, 11.45.

(ii) The above reaction was repeated in a mixture of acetic anhydride (5.0 ml) and acetic acid (5.0 ml). When the reaction mixture was allowed to cool, a pale-yellow product (0.26 g), m.p. 308-9° separated. Physical and chemical properties of this compound (A') were identical to those of compound (A) except that the i.r. spectrum of (A') had a broad absorption between 2500 and 3300 cm^{-1} (NH or OH) and a strong absorption at 1640 cm^{-1} (C=O). Mixed m.p. of (A) AND (A') showed no depression.

When a sample (0.2 g) of either (A) or (A') was acetylated with acetic anhydride, it yielded an acetylated product (0.19 g), m.p. 153-4°.

I.r. spectrum (nujol): 1664 and 1730 (C=O) cm^{-1}; No NH absorption.

Mass Spectrum: 317 (M^+, 67%), 275 (100%), 274 (76%), 43 (48%).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.98; H, 4.77; N, 13.26.

Found: C, 71.82; H, 4.69; N, 12.91.

(iii) Acetylation of spiro[(1-hydroxindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (0.5 g) with acetic anhydride (10 ml) as described above gave a pale-yellow powder (0.48 g), m.p. 124-8°. Attempted crystallization twice from ethanol/water failed to purify this compound which was identified as spiro[(1,x-diacetyloxyindoline)-2,4'-(1',3'-diphenyl-1*H*-pyrazolin-5'-one)] (364).

I.r. spectrum (nujol): 1662 (cyclic amide C=O); 1725 (lactam C=O); 1759 (ester C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (DMSO-d_6): δ2.29 (3H, s, $OCOCH_3$); 2.45 (3H, s, $NCOCH_3$); 3.59 (2H, br. s, CH_2); 7.0-8.3 (13H, m, aromatic protons).

Mass spectrum: 439 (M^+, 16%), 397 (60%), 355 (52%), 327 (28%).

(iv) Cold acetic anhydride (3.0 ml) was added to a solution of the spiro (N-hydroxyindoline)pyrazolone (338, 0.3 g) in cold pyridine (3.0 ml) and the mixture was kept for 24 hours at -10°. A colorless crystalline solid (0.26 g), m.p. 92-3° was separated. This was identified as spiro[(1-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (349).

I.r. spectrum (nujol): 1790 (N-acetyloxy C=O); 1723 (lactam C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (measured directly after dissolving in cold $CDCl_3$ or DMSO-d_6): δ2.05 (3H, s, CH_3); 2.14 (3H, s, CH_3); 3.38 (2H, doublet of doublets, J=16.5 Hz, CH_2); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53.

Found: C, 68.31; H, 5.23; N, 12.81.

On some occasions when the above reaction was repeated, the N-acetyloxy product (349) did not precipitate during the reaction.

When this was so, the reaction mixture was diluted with ethanol (5 ml) and poured with stirring into ice-cold water (100 ml). This yielded the spiro(N-acetoxyindoline)pyrazolone (349) as white powder (0.31 g), m.p. 90-2°. Crystallization of this powder from ethanol (or methanol) resulted in the formation of an off-white crystalline solid (0.09 g), m.p. 306-7°, the i.r. spectrum of which was identical with the previously isolated, compound (A). When the mother liquor was concentrated and allowed to stand, spiro[(5-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346d) was deposited as pale-yellow solid (0.13 g), m.p. 117-18°.

(v) Spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (0.3 g) was acetylated with acetic anhydride and pyridine as described above in (iv). After keeping the reaction mixture for 24 hours at 0°, it was diluted with ethanol (3 ml) and poured into ice-cold water with stirring. The white powder collected (0.32 g), m.p. 90-1° (sintered at 65°) was identified as spiro[(1-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (361).

I.r. spectrum (nujol): 1792 (N-acetoxy C=O); 1725 (lactam C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (measured directly after dissolving in cold DMSO-d_6): δ2.0 (3H, s, $OCOCH_3$); 3.6 (2H, doublet of doublets, J=16.0 Hz, CH_2); 6.9-9.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.81; N, 10.57.

Found: C, 72.19; H, 4.83; N, 10.26.

Heating the above compound (0.3 g) in ethanol produced a reddish solution. This was added, with stirring, to ice-cold water

(100 ml) and the brown precipitate formed was collected and dried. Crystallization twice from benzene/petroleum ether (40-60°) gave a yellow solid (0.12 g), m.p. 115-7° Which was partially identified as spiro[(x-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (362).

I.r. spectrum (nujol): 1723 (lactam C=O); 1750 (ester C=O); 3340 (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.23 (3H, s, $OCOCH_3$); 3.58 (2H, doublet of doublets, J=15.5 Hz, CH_2); 5.7 (1H, br. s, exchanged with D_2O, NH); 6.7-8.3 (13H, m, aromatic protons).

Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.81; N, 10.57.

Found: C, 72.11; H, 4.99; N, 10.29.

b. Reaction with acetyl chloride

To a solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in hot dry benzene (10 ml), acetyl chloride (1.0 ml) was added and the mixture heated under reflux for ten hours. The resulting red solution was evaporated to dryness, leaving a dark oil which was dissolved in hot ethanol. Cooling gave a small quantity (0.07 g) of a product as red needles, m.p. 209-10°. This compound remains unidentified. Its hydrolysis is described below.

I.r. spectrum (nujol): 1688 and 1712 cm^{-1}; no NH or OH absorption.

N.m.r. spectrum ($CDCl_3$): δ2.44 (3H, s, CH_3); 2.48 (3H, s, CH_3); 7.0-8.2 (8H, m, aromatic protons); 9.8 (1H, d, J=8 Hz, ?).

Mass spectrum: See Fig. 5.

Anal. Calcd. for $C_{19}H_{15}N_3O_7$: C, 68.53; H, 4.54; N, 12.61.

Found: C, 68.74; H, 4.95; N, 12.75.

After the above product was collected, the filtrate was concentrated and from it pale-orange crystals (0.3 g), m.p. 188-9° separated. This was spiro[(7-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (370).

I.r. spectrum (nujol): 1728 (C=O); 3295 (N–H) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ 2.1 (3H, s, CH_3); 3.46 (2H, doublet of doublets, J=16 Hz, CH_2); 4.58 (1H, br. s, exchanged with D_2O, NH); 6.55-8.1 (8H, m, aromatic protons).

Mass spectrum: 311 (M^+, 100%), 294 (9%), 283 (60%).

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48.
Found: C, 65.31; H, 4.66; N, 13.11.

A sample (60 mg) of this unidentified acetate, m.p. 209-10° described above was suspended in 10% aqueous sodium hydroxide (5.0 ml) and stirred for two hours. The resulting yellow solution was filtered, acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract yielded a yellow solid (40 mg), m.p. 179-80° (ethanol).

I.r. spectrum (nujol): 2000-3300 br. (OH); 1637 (C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ 2.58 (3H, s, CH_3); 4.0-5.2 (1H, br.s, exchanged with D_2O, OH); 8.6 (1H, d, J=8 Hz, ?); 6.7-8.1 (8H, m, aromatic protons).

Mass spectrum: 291 (M^+, 72%), 205 (8%), 200 (8%), 186 (10%), 178 (10%), 158 (59%), 130 (24%), 120 (100%).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.1 H, 4.49; N, 14.43.
C, 69.73; H, 4.51; N, 14.02.

c. Reaction with p-chlorobenzoyl chloride

A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-

1'-phenyl-1*H*-pyrazolin-5'-one)] (0.8 g) in dry pyridine (5.0 ml) was cooled in an ice-bath at 0-5°. *p*-Chlorobenzoyl chloride (0.5 g) in pyridine (5.0 ml) was added dropwise with stirring. After stirring at the same temperature for one hour, the mixture was poured into ice-water to give a pale-yellow semi-solid which solidified on further cooling. The i.r. spectrum of this product displayed C=O absorptions at 1790, 1765 and 1725 cm^{-1}. A solution of this product in ether was shaken with 10% hydrochloric acid, 10% sodium carbonate, and then with water. The dried (Na_2SO_4) ethereal solution was evaporated *in vacuo* to yield a white solid (0.51 g). This was recrystallized from cold ethanol into colorless crystals, m.p. 196-7° identified as *spiro[(x-benzoyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (373)*.

I.r. spectrum (nujol): 3380 (N—H); 1732 (ester C=O); 1712 (lactam C=O) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.15 (3H, s, CH_3); 3.45 (2H doublet of doublets, J=17 Hz, CH_2); 4.47 (1H, br., exchanged with D_2O, NH); 6.6-8.3 (12H, m, aromatic protons).

Mass spectrum: 431 (M^+, 88%), 414 (2%), 403 (13%), 292 (29%), 139 (100%), 111(18%).

Anal. Calcd. for $C_{24}H_{18}ClN_3O_3$: C, 66.74; H, 4.20; N, 9.73.
Found: C, 66.56; H, 4.51; N, 9.98.

d. *Reaction with p-toluenesulfonyl chloride*

Method A: A solution of *p*-toluenesulfonyl chloride (0.65 g) in pyridine (5 ml) was added to an ice-cold solution of 1.0 g of the spiro (N-hydroxyindoline)pyrazolone (338) in pyridine (5 ml). The mixture was stirred at 0-5° for two hours then warmed on a steam bath for

15 minutes. After cooling to room temperature, it was poured into a cold mixture of 5 ml hydrochloric acid and 100 ml water. The yellow precipitate formed was collected, and dried then dissolved in benzene. A small amount (0.09 g) of pale-yellow crystals, m.p. 306-8° separated. This was found (i.r. and mixed m.p.) to be the dehydrated compound (A) isolated earlier (p. 276). The filtrate remaining after the removal of this product was evaporated to yield a yellow solid which was difficult to crystallize. This was placed on a silica gel column and eluted with petroleum ether (30-60°) then benzene (100 ml). Evaporation of the latter solution gave a pale-yellow residue which crystallized from ethanol and yielded the previously described (p. 264) spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346a) as colorless crystals (0.18 g) m.p. 150-2°. Continued elution with chloroform (80 ml) gave a yellow oil which solidified when triturated with ethanol. Recrystallization from the same solvent gave spiro[(x-p-toluene-sulfonylindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (374) as an off-white solid (0.14 g), m.p. 162-4°.

I.r. spectrum (nujol): 1720 (C=O); 3350, br. (NH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ 2.09 (3H, s, CH_3); 2.45 (3H, s, CH_3)
3.35 (2H, doublet of doublets, J=16.5 Hz, CH_2); 5.0 (1H, br. s, exchanged with D_2O NH); 6.5-8.3 (12H, m, aromatic protons).

Mass spectrum: 447 (M+, 37%), 419 (6%), 292 (45%).

Anal. Calcd. for $C_{24}H_2N_3O_4S$: C, 64.61; H, 4.73; N, 9.39.
Found: C, 63.97; H, 4.89; N, 9.08.

Method B: To a stirred, ice-cold solution of the spiro(N-hydroxy-indoline)pyrazolone (338, 1.0 g) in ether (120 ml) were added dropwise and at equal rates solutions of p-toluene sulfonyl chloride (0.65 g) in chloroform (20 ml) and triethylamine (0.35 g) in ether (15 ml). After addition, stirring was continued for two hours then the solution was filtered and concentrated to give a dark-brown semi-solid which was difficult to crystallize. When spotted on a silica gel plate and eluted with benzene/chloroform (1:2), the product was found to be a mixture of at least five compounds. This was not investigated further.

(6) Methylation:

A) **Excess** diazomethane in ether was added to a stirred solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.8 g) in methanol (80.0 ml). After standing for 24 hours at room temperature, the solvent was removed in vacuo leaving a pale-yellow solid. Its infrared spectrum was identical to that of the starting material.

B) The above reaction was repeated in the presence of a catalytic amount (2 ml) of boron trifluoride (14% solution in methanol). The resulting green solution was allowed to stand for 24 hours at room temperature then evaporated under reduced pressure leaving a green precipitate. Crystallization of this crude product from ethanol yielded a white crystalline solid (0.68 g), m.p. 137-8°. This was found to be the previously identified (p. 274) spiro[(5-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346b).

C) The reaction described above was repeated in dioxane (80.0 ml) using alcohol-free ethereal solution of diazomethane and boron trifluoride-ether complex (1 ml). Solvents were removed under reduced pressure leaving a green residue which was extracted with chloroform. Evaporation of the chloroform solution yielded a green powder, the i.r. spectrum of which displayed a C=O absorption at 1720 cm^{-1} and no NH or OH absorption. When this solid was dissolved in ethanol, it crystallized as a dark-yellow solid (0.21 g), m.p. 308-9° identical to the unidentified compound (A) isolated earlier (p. 276). A mixed melting point of the isolated compound and compound (A) showed no depression.

The filtrate left after isolation of the above product was concentrated to a dark semi-solid which did not crystallize. This was not investigated further.

D) Methyl iodide (1.0 g) in methanol (5.0 ml) was added to to a solution of the spiro(N-hydroxyindoline)pyrazolone (338, 0.5 g) in methanol (15.0 ml) containing 0.2 g of sodium. The mixture was heated under reflux for three hours during which time a yellow color had developed. The solvent was evaporated and the residue extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a yellow solid which was crystallized from methanol and yielded spiro [(1-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (375) as pale-yellow crystals (0.39 g), m.p. 112-4°.

I.r. spectrum (nujol): 1719 (C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum ($CDCl_3$): δ1.96 (3H, s, C CH$_3$); 3.8 (3H, s, O-CH$_3$); 3.27 (2H doublet of doublet, J=17 Hz, CH$_2$); 6.8-8.3 (9H, m, aromatic protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67.
Found: C, 70.41; H, 5.38; N, 13.29.

Preparation of 3-methyl-5-phenylpyrazolo-[4,5-c] carbostyril (350)

This compound was prepared according to the method reported by Vul'fson and Zhurin (1962) in 85% yield. M.p. 276-7° (methanol) and 275-6° (ethanol). The reported m.p. are 277-8° and 268-9° respectively.

I.r. spectrum (nujol): 1666 (C=O); 200-3220 (NH) cm^{-1}.

N.m.r. spectrum* (DMSO-d_6): δ2.61 (3H, s, CH_3); 13.2 (1H, br. s, NH or OH); 6.9-8.7 (9H, m, aromatic protons).

General Procedure for the Preparation of spiro[(1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-substituted-1',2',3',4'-tetrahydroquinolines)] (337).

A hot solution of the 4-(2-aminobenzyl)-1-phenyl-2-pyrazolone (0.5 g) in either methanol or ethanol (15.0 ml) was mixed with a quantitative amount of the appropriate aldehyde. The reaction mixture was heated under reflux for about one hour. Upon cooling, many of the title compounds separated and were recrystallized from ethanol. In some cases, the reaction mixture was concentrated to about half its volume then diluted with water. The precipitate was washed with water, dried and recrystallized from either methanol or ethanol as colorless crystals.

A similar reaction was carried out using acetone instead of an aldehyde. In this instance, the solvent used was either ethanol or butanol. Suitable reaction times were found to be 24 hours when ethanol was the solvent, or 4-6 hours when butanol was employed.

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* The n.m.r. spectrum of compound (350) crystallized from methanol had an additional methyl signal at δ3.5 which is attributed to the solvent of crystallization.

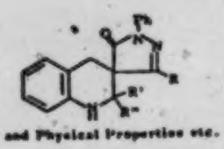
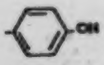
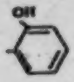
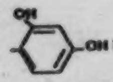
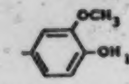
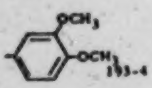
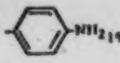
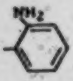
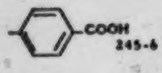
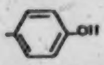
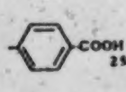


Table 6. Elemental Analyses and Physical Properties etc. of the Spiro(Tetrahydroquinoline) Pyrazolones (337a-r).

Compound	R	R'	R"	m.p. (° C)	% Yield	Molecular formula	Analyses % Calcd. C	H	N	Found C	H	N
337 a	CH_3	H	CH_3	149-50	84	$C_{19}H_{19}N_3O$	74.72	6.27	13.76	74.61	6.04	13.57
b	CH_3	H	C_2H_5	143-4	81	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	75.40	6.71	12.98
c	CH_3	H	Ph	146-7	77	$C_{24}H_{21}N_3O$	78.45	5.76	11.43	78.73	5.75	11.10
d	CH_3	H		212-3	85	$C_{24}H_{21}N_3O$	75.15	5.52	10.96	74.82	5.51	10.99
e	CH_3	H		176-8	95	$C_{24}H_{21}N_3O_2$	75.15	5.52	10.96	74.90	5.47	11.00
f	CH_3	H		180-2	73	$C_{24}H_{21}N_3O_3$	72.16	5.30	10.52	71.69	5.41	10.81
g	CH_3	H		181-2	98	$C_{25}H_{23}N_3O_3$	72.62	5.61	10.16	72.38	6.07	10.02
h	CH_3	H		193-4	96	$C_{26}H_{25}N_3O_3$	73.05	5.89	9.83	72.91	5.93	9.81
i	CH_3	H		193-5	89	$C_{24}H_{22}N_4O$	75.37	5.80	14.65	75.44	5.73	14.13
j	CH_3	H		165-6	95	$C_{24}H_{22}N_4O$	75.37	5.80	14.65	75.31	5.49	14.32
k	CH_3	H		245-6	79	$C_{25}H_{21}N_3O_3$	72.98	5.15	10.21	73.22	5.02	10.03
l	Ph	H	CH_3	174-5	93	$C_{24}H_{21}N_3O$	78.45	5.76	11.43	78.47	5.60	11.60
m	Ph	H	C_2H_5	160-2	96	$C_{25}H_{23}N_3O$	78.71	6.07	11.02	78.63	6.04	11.07
n	Ph	H	Ph	210-2	96	$C_{29}H_{23}N_3O$	81.07	5.39	9.78	81.12	5.43	9.80
o	Ph	H		237-9	95	$C_{29}H_{23}N_3O_2$	78.18	5.20	9.43	78.39	5.00	9.72
p	Ph	H		253-4	90	$C_{30}H_{23}N_3O_3$	76.09	4.89	8.87	75.77	5.01	8.76
q	CH_3	CH_3	CH_3	148-51	90	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	-	-	-
r	Ph	CH_3	CH_3	198-9	84	$C_{25}H_{23}N_3O$	78.71	6.07	11.02	78.92	5.94	10.81

The physical constants and elemental analyses of the compounds prepared by this method are compiled in Table 6. Their i.r. spectra displayed N–H absorption bands around 3400 and C=O bands around 1700 cm^{-1}. Each n.m.r. spectrum showed, in addition to the signals ascribable to the aromatic protons and the different substituents at C-3 of the tetrahydroquinoline ring, a 2-proton doublet of doublets around $\delta 3.2$ with J value ~17 Hz (CH_2), a one proton signal near $\delta 4.5$ ($-\overset{|}{C}\underline{H}R$) and a D-exchangeable N–H signal of variable chemical shift. Those of the 3-methylpyrazolone derivatives also contained a methyl signal around $\delta 2.0$. The mass spectra of some of these compounds were recorded and are shown in Figs. 6 and 7.

Condensation of 4-(2-aminobenzyl)-1-phenyl-2-pyrazoline-5-ones (321a, b) with formaldehyde and salicylaldehyde.

A) A mixture of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) and formaldehyde (1.0 ml of 40% formalin solution) in methanol (15.0 ml) was heated under reflux for two hours. The solvent was evaporated giving an oily residue which was difficult to crystallize. The i.r. spectrum of this oil had a C=O absorption at 1707 cm^{-1} and an NH or OH absorption.

B) When 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5'-one (0.5 g) was treated similarly with formaldehyde, it yielded a white crystalline solid (0.26 g), m.p. 92-3° which was not identified. I.r. spectrum (nujol): 1710 (C=O) cm^{-1}, no NH or OH absorption. Anal. Found (Average): C, 78.27; H, 6.21; N, 8.80.

C) A solution of 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) in hot ethanol (15.0 ml) was mixed with salicylaldehyde (0.18 g). The mixture was heated under reflux for one hour during which time its color turned dark-yellow. When cooled, a dark-yellow solid separated. This was recrystallized from ethanol giving 1,3-diphenyl-4-[2-(o-hydroxybenzylidene)aminobenzyl]-2-pyrazolin-5-one (385) as yellow crystals (0.55 g), m.p. 199-200°.

I.r. spectrum (nujol): 2100-3120 br. (NH and OH); 1610; 1593; 1581; 1568 cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ3.3 (2H, doublet of doublets, J=16 Hz, CH_2); 5.3 (1H, s, CH); 6.2 (1H, br. s, exchanged with D_2O, NH); 6.5-8.2 (18H, m, aromatic protons); 9.38(1H, br. s, exchanged with D_2O, OH).

Mass spectrum: See Fig. 8.

Anal. Calcd. for $C_{29}H_{23}N_3O_2$: C, 78.18; H, 5.20; N, 9.43.
Found: C, 77.98; H, 5.32; N, 9.31.

Reactions of spiro(tetrahydroquinoline)pyrazolones (337).

A. Acetylations:

Each of the spiro(tetrahydroquinoline)pyrazolones (337b, c, e, n and o) (0.3 g) was acetylated by heating with excess acetic anhydride (5 ml) for 15 minutes. The reaction mixture was poured while stirring into ice-water and the resulting product was either collected and crystallized or extracted with ether. Ethanol was the crystallization solvent used for all these products.

Table 7 contains the elemental analyses of the acetylated compounds and some of their physical constants. The i.r. spectra of all compounds contained C=O absorption bands around 1665 (cyclic amide) and 1710 (lactam) and were devoid of any N—H absorption.

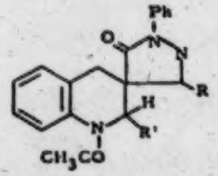
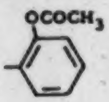
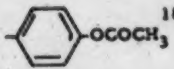


Table 7 : Elemental analyses and Physical Properties etc. of some acetylated spiro(tetrahydroquinoline pyrazolones.

Compound	R	R'	m.p. °C	% Yield	Molecular formula		Analyses %		
							C	H	N
397	CH_3	C_2H_5	220-1	78	$C_{22}H_{23}N_3O_2$	Calcd. Found	73.11 72.79	6.41 6.28	11.63 -
395	CH_3	Ph	223-4	80	$C_{26}H_{23}N_3O_2$	Calcd. Found	76.26 76.59	5.66 5.60	10.26 9.91
394	CH_3		205-6	84	$C_{28}H_{25}N_3O_4$	Calcd. Found	71.93 72.37	5.39 5.23	8.99 9.01
393	Ph	Ph	218-9	91	$C_{31}H_{25}N_3O_2$	Calcd. Found	78.96 79.01	5.34 5.33	8.91 8.87
391	Ph		188-9	88	$C_{33}H_{27}N_3O_4$	Calcd. Found	74.84 74.91	5.14 5.23	7.93 7.78

Compounds (391) and (394) contained in addition a C=O band around 1765 (ester). Important signals in the n.m.r. spectra (in DMSO-d_6 or $CDCl_3$) of these acetyl derivatives are presented in Table 3 in the discussion part of this thesis.

B. Reductions:

Method A: Reduction with sodium borohydride in dioxane:

(i) A solution of spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline)] (337a, 0.5 g) in dioxane (15 ml) was added dropwise to a stirred solution of sodium borohydride (0.5 g) in water (5 ml). After addition was completed, stirring was continued for thirty minutes then the reaction mixture was acidified with dilute acetic acid and diluted with water. Crystallization of the resulting precipitate from ethanol gave 4-(2-ethylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398a) as white crystalline powder (0.33 g), m.p. 181-2°.

I.r. spectrum (nujol): 2100-3500, br. (OH) with maximum at 3380 (NH); 1620 (bonded C=O?) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ1.02 (3H, t, CH_3); 1.91 (3H, s, CH_3); 3.4 (2H, s, CH_2); 3.6 (2H, q, CH_2); 6.4-7.4 (11H, m, aromatic protons included 1-2 exchanged with D_2O, NH and pyrazolone proton).

Mass spectrum: See Fig. 9.

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67.

Found: C, 74.11; H, 7.03; N, 13.22.

(ii) Spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (337b, 0.5 g) was reduced in a similar manner to yield 4-(2-n-propylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398b) as white crystals (0.31 g), m.p. 149-50°.

I.r. spectrum (nujol): 2040-3400, br. (OH) with maximum at 3380 (NH); 1617 (bonded C=O?) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ0.7-1.75 (5H, m, CH_2CH_3); 2.05 (3H, s, CH_3); 3.3 (2H, s, CH_2); 3.45 (2H, t, NCH_2); 6.3-7.6 (10H, m, aromatic protons and pyrazoline proton); 9.02 (1H, br. s, exchanged D_2O, NH).

Mass spectrum: See Fig. 9.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.76; H, 7.21; N, 13.07.

Found: C, 74.57; H, 7.55; N, 12.90.

(iii) Similarly, spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-phenyl-1',2',3',4'-tetrahydroquinoline)] (337c, 0.5 g) was reduced as described above giving 4-(2-benzylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398c) as white crystals (0.39 g), m.p. 155-6°.

I.r. spectrum (nujol): 2000-3360, br. with maximum at 3305 (N—H), 1612 (bonded C=O?) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ1.88 (3H, s, CH_3); 3.3 (2H, s, CH_2); 4.25 (2H, s, CH_2); 6.4-7.8 (16 H, m, aromatic protons included two exchanged with D_2O, NH and pyrazolone ring proton).

Mass spectrum: See Fig. 9.

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 77.99; H, 6.27; N, 11.37.

Found: C, 77.56; H, 6.52; N, 10.98.

(iv) The spiro(tetrahydroquinoline)pyrazolone (337e, 0.5 g) was reduced as described above yielding a white crystalline product (0.35 g), m.p. 180-1° identified as 4-[2-(o-hydroxybenzyl)-aminobenzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (398d).

I.r. spectrum (nujol): 2100-3300, br. (OH) with maximum at 3290 (NH);

1608 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.1 (3H, s, CH_3); 3.5 (2H, s, CH_2); 4.33 (2H, s, CH_2); 6.4-8.0 (H, m, aromatic proton included one exchanged with D_2O, pyrazolone proton); 9.4 (1H, br., OH).

Anal. Calcd. for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90.

Found: C, 75.03; H, 6.33; N, 11.17.

Method B: Reduction with lithium aluminum hydride in ether.

(i) A solution of the spiro(tetrahydroquinoline)pyrazolone (337a, 0.75 g) in ether (50 ml) was slowly added, with stirring, to a mixture of lithium aluminum hydride (0.15 g) and ether (20 ml). After refluxing for ten hours, water was added dropwise to the cooled reaction mixture until the evolution of hydrogen ceased. The solution was made alkaline by the addition of 30% aqueous sodium hydroxide (~20 ml) then the mixture was extracted with ether. Evaporation of the dry (Na_2SO_4) ether extract gave a white powder which crystallized from ethanol as a white solid (0.14 g), m.p. 178-9°. This compound is tentatively identified as spiro[(3-methyl-1-phenyl-1*H*-pyrazoline)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline)] (399a).

I.r. spectrum (nujol): 3470; 3390; 1595 cm^{-1}.

Mass spectrum: 291 (M^+, 2%), 263 (97%), 248 (10%), 171 (100%).

Anal. Calcd. for $C_{19}H_{21}N_3$: C, 78.31; H, 7.21; N, 14.42.

Found: C, 77.97; H, 7.03; N, 13.91.

The basic solution was neutralized with 30% sulfuric acid then extracted with ether. From the ethereal extract, 4-(2-ethylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398a) was separated as off-white crystals (0.29 g), m.p. 181-2°. Comparison of the infrared spectrum of this compound with that of an authentic sample prepared earlier (p. 291) proved identity.

(ii) The spiro(tetrahydroquinoline)pyrazolone (337b, 0.8 g) was reduced similarly yielding from the basic solution, a basic product (0.12 g) as a pale-yellow solid, m.p. 170-1°. This is tentatively identified as spiro[(3-methyl-1-phenyl-1H-pyrazoline)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (399b).

I.r. spectrum (nujol): 3405; 3290 br.; 1600 cm^{-1}.

Mass spectrum: 305(M^+, 25%), 303 (9%), 276 (13%), 274 (34%), 263 (43%), 171 (65%), 118 (100%).

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76.

Found: C, 78.40; H, 7.61; N, 13.51.

Neutralization of the basic solution with 30% sulfuric acid then extraction with ether yielded the 4-(2-n-propylaminobenzyl)-pyrazolone (398b) which crystallized from ethanol as pale-orange needles (0.2 g), m.p. 147-8°. The infrared spectrum of this product was identical with that of an authentic sample of (398b) prepared earlier (p.291).

(iii) The spiro(tetrahydroquinoline)pyrazolone (337c, 1.0 g) was reduced with lithium aluminum hydride (0.1 g) in ether as described in preparation (i). When the basic solution was extracted with ether and the dried (Na_2SO_4) ether extract evaporated, a white powder was obtained. Fractional crystallization of this powder from ethanol, yielded two compounds. The infrared spectrum of the more soluble compound (0.21 g) was identical with that of the starting material. The other compound (0.09 g) was recrystallized from the same solvent giving white solid, m.p. 205-6° which is tentatively identified as spiro[(3-methyl-1-phenyl-1H-pyrazoline)-4,3'-(2'-phenyl-

1',2',3',4'-tetrahydroquinoline](399c).

I.r. spectrum (nujol): 3380; 3290, br.; 1597 cm^{-1}.

Mass spectrum: 353 (M$^+$, 7%), 351 (100%), 350 (29%), 336 (8%), 274 (22%), 193 (36%).

Accurate mass measurements: 353.1888, $C_{24}H_{23}N_3$ requires 353.1892; 351.1730, $C_{24}H_{21}N_3$ requires 351.1736.

Anal. Calcd. for $C_{24}H_{23}N_3$: C, 81.57; H, 6.56; N, 11.89.
Found: C, 81.08; H, 6.91; N, 12.03.

The basic solution was neutralized with 30% sulfuric acid then extracted with ether. Evaporation of the ethereal extract yielded off-white crystals (0.32g), m.p. 154-5° (ethanol). The infrared spectrum of this compound indicated that it was the previously identified (p. 292) 4-(2-benzylaminobenzyl)pyrazolone (398c).

Method C: Reduction with lithium aluminum hydride in tetrahydrofuran.

A solution of the spiro(tetrahydroquinoline)pyrazolone (337a, 0.75 g) in freshly distilled, dry tetrahydrofuran (30 ml) was added dropwise to a stirred solution of lithium aluminum hydride (0.15 g) in tetrahydrofuran (10 ml). The mixture was refluxed for ten hours then the solvent was removed by distillation and replaced with fresh ether (30 ml). Water was added dropwise until the evolution of hydrogen ceased. Aqueous sodium hydroxide (30%, ~10 ml) was added then the alkaline solution was extracted with ether. The ether solution was dried and evaporated to yield a white solid which was crystallized from ethanol giving white crystals (0.29 g), m.p. 179-80° identified, by infrared comparison, as the previously identified spiro-pyrazoline (399a).

Neutralization of the aqueous basic solution with dilute hydrochloric acid followed by extraction with ether, gave a small amount (45 mg) of the previously identified 4-(2-ethylaminobenzyl)pyrazolone (398a).

Method D: Reduction by lithium aluminum hydride and aluminum chloride in ether

A method similar to that described by Nystrom and Berger (1958) was followed. A solution of granular aluminum chloride (0.67 g) in ether (20 ml) was added rapidly to a stirred solution of lithium aluminum hydride (0.19 g) in ether (20 ml). Five minutes later, a solution containing the spiro(tetrahydroquinoline)pyrazolone (337c, 1.8 g), and granular aluminum chloride (0.67 g) in ether (40 ml) was added dropwise and the mixture was refluxed for four hours. Water was added dropwise until the evolution of hydrogen ceased then the reaction mixture was made alkaline with 30% sodium hydroxide and extracted with ether. Sulfuric acid (30%) was added to the aqueous solution until it became neutral then acidic and the solution was extracted with ether each time. During acidification a solid separated out between the aqueous and organic layers. This was collected and crystallized from ethanol yielding an off-white crystalline powder (1.3 g), m.p. 155-6°. The i.r. spectrum of this product was identical with that of 4(2-benzylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398c) prepared earlier (p.292). Evaporation of the ether extracts of the alkaline, neutral and acidic aqueous solutions yielded small amounts (total 0.12 g) of the same product, m.p. 155-6°. A comparison of i.r. spectra indicated identity with the compound (398c) described immediately above.

Reactions of 1,3-diphenyl-4-[2-(o-hydroxybenzylidene)aminobenzyl]-2-pyrazolin-5-one (385)

A. Attempted Reduction:

A solution of the title compound (0.5 g) in dioxane (15 ml) was added dropwise to a stirred solution of sodium borohydride (0.5 g) in water (5 ml). Stirring was continued for thirty minutes after the addition was completed then the solution was acidified with acetic acid and diluted with water. The resulting white precipitate (0.33 g) did not crystallize.

B. Methylation:

To an ice-cooled solution of the title compound (0.5 g) in dilute sodium hydroxide (15 ml), dimethylsufate (1.0 ml) was added dropwise with stirring then the mixture was heated on a water bath for one hour. The resulting oily residue was extracted with chloroform. This extract was washed with dilute sodium hydroxide then with water and dried. Evaporation of the organic solvent yielded an off-white solid (0.45 g), m.p. 128-32° which could not be purified by fractional crystallization from various solvents but which contains appreciable amounts of 1,3-diphenyl-4[2-(o-methoxybenzylidene)aminobenzyl]-2-methyl-3-pyrazolin-5-one (387).

I.r. spectrum (nujol): 1660 (C=O) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.98 (3H, s, N–CH_3); 3.37 (2H, s, CH_2); 3.87 (3H, s, OCH_3); 6.4-7.9 (~18H, m, aromatic protons).

Mass spectrum: 473 (M^+, 4%), 472 (9%), 458 (8%), 383 (80%), 118 (100%).

C. Acetylation:

The title compound (0.3 g) was heated under reflux with acetic anhydride (5 ml) for 15 minutes, then the reaction mixture was poured into ice-water (30 ml). The resulting precipitate was crystallized from ethanol yielding spiro{[1,3-diphenyl-1*H*-pyrazolin-5-one]-4,3'-acetyl-2'-(*o*-acetoxyphenyl)-1',2',3',4'-tetrahydroquinoline]} (392) as colorless needles (0.22 g), m.p. 240-1°.

I.r. spectrum (nujol): 1764 (ester C=O); 1720 (lactam C=O); 1666 (amido C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ1.93 (3H, s, $OCOCH_3$); 2.24 (3H, s, $NCOCH_3$); 3.26 (2H, doublet of doublets, J=15 Hz, CH_2); 6.3-8.3 (14H, m, C_2 H and aromatic protons).

Anal. Calcd. for $C_{33}H_{27}N_3O_4$: C, 74.84; H, 5.14; N, 7.93.
Found: C, 75.21; H, 5.03; N, 7.99.

II. REDUCTIONS OF 4-(2-NITROPHENYLTHIO)-2-PYRAZOLINE-5-ONES

Preparation of 4-(2-nitrophenylthio)-2-pyrazolin-5-ones(400)

Bis-(2-nitrophenyl)disulfide

This compound was prepared from o-chloronitrobenzene (31.5 g), sodium sulfide (36 g) and sulfur (4.8 g) according to the method reported by Bogart and Stull (1928). The product was crystallized from ethanol as yellow crystals (20 g), m.p. 193-5°. Reported (Bogart and Stull, 1928) m.p. 192-5°.

2-Nitrobenzenesulfenyl chloride (404)

Was prepared following the procedure described by Hubacher (1935). Dry chlorine gas was bubbled through a warmed suspension of bis-(2-nitrophenyl)disulfide (15.4 g) and iodine (50 mg) in carbon tetrachloride (60 ml) for one to two hours. When the reaction mixture was cooled, it yielded the title compound as a yellow solid which was recrystallized from carbon tetrachloride as yellow needles (14.8 g), m.p. 73-4° as reported (Hubacher, 1935).

3-Methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a)

This compound was prepared according to the method described by Coutts et al (1966). A solution of 2-nitrobenzenesulfenyl chloride (6.0 g) in acetonitrile (40 ml) was added to a suspension of 3-methyl-1-phenyl-2-pyrazolin-5-one (6.0 g) in the same solvent (40 ml) and the mixture was stirred under reflux for four hours. When cooled, the title compound was separated as yellow crystals (9.2 g), m.p. 207-9° (decomp.) from ethanol. Reported (Coutts et al, 1966) m.p. 207°.

I.r. spectrum (nujol): 3040-3730, br. with a maximum at 3420 (OH), 1513 and 1332 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.17 (3H, s, CH_3); 7.1-8.5 (9H, m, aromatic protons); 11.0-12.5 (1H, br. s, OH).

4-(2-Nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (400b)

Was obtained as dark yellow solid (2.9 g, m.p. 183-4°, decomp.) from 2-nitrobenzesulfenyl chloride (1.61 g) and 1,3-diphenyl-2-pyrazolin-5-one (2.0 g) using the same method as that described above for the preparation of (400a). Reported (Coutts et al, 1966) m.p. 182-3° (decomp.).

I.r. spectrum (nujol): 2100-3150, br. with maximum at 3080 (OH); 1530 and 1337 (NO_2) cm^{-1}

Reductions of 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a)

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution

Following the general procedure outlined on p. 245, a solution of the title compound (2.0 g) in 10% aqueous sodium hydroxide (50 ml) was reduced with sodium borohydride and palladium-charcoal. The reaction mixture was filtered and the filtrate was acidified, over ice, with dilute acetic acid yielding a copious cream colored precipitate (1.9 g), m.p. 140-6° (poroduct E). This product was purified by dissolving it in dilute sodium hydroxide, filtering and acidifying the filtrate with dilute acetic acid.

I.r. spectrum (nujol): 2200-3300, br. (OH); 3300-3400, br. (NH).

N.m.r. spectrum (DMSO-d_6): δ2.09 (3H, br.s, CH_3); 6.3-8.1 (12H, m, aromatic protons which included 2 exchanged with D_2O).

Mass spectrum: 297 (M^+, 11%), 295 (29%), 267 (6%), 93 (100%).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: N, 14.13.

Found: N, 13.86.

When this compound (1.8 g) was dissolved in ethanol and filtered, a pale-yellow granular solid (0.61 g), m.p. 215-7°, precipitated during the filtration. This product (F) was soluble in aqueous sodium hydroxide solution but insoluble in ethanol, methanol, ether, benzene or chloroform. Acidification of the sodium hydroxide solution of (F) with acetic acid gave the ethanol-soluble product (E). The equivalent weight of (F) was determined (by dissolving an accurately weighed quantity in a known excess of 0.1N sodium hydroxide and back titration with 0.1N hydrochloric acid using methyl orange as indicator) and was found to be 148.

I.r. spectrum (nujol): 2100-3300, br. with weak maxima at 2600, 2660 and 3070 (OH and SH); 3370 (NH); 1626 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.05 (3H, s, CH_3); 6.3-8.0 (12H, m, aromatic protons which included 2 or 3 protons exchanged with D_2O, NH, SH and pyrazolone proton).

Mass spectrum: See Fig. 10.

Accurate mass measurements: 297.0919, $C_{16}H_{15}N_3OS$ requires 297.0921; 279.0823 $C_{16}H_{13}N_3S$ requires 279.0830; 264.1138 $C_{16}H_{14}N_3O$ requires 264.1136.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13.

Found: C, 64.78; H, 4.91; N, 14.39.

Both products (E) and (F) were identified as 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-pyrazolin-5-one (406).

[Compound erroneously identified by Pound (1970)].

When the mother liquor remaining after the removal of the above product (406) was concentrated and allowed to stand, pale-yellow needles (0.23 g), m.p. 153-4° separated. This was spiro-[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (403). Reported (Pound, 1970) m.p. 154-6°.

I.r. spectrum (nujol): 3275 (N—H); 1705 (C=O) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.22 (3H, s, CH_3); 4.98 (1H, br. s, exchanged with D_2O, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: See Fig. 23.

Accurate mass measurements: See Table 5.

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23.

Found: C, 65.23; H, 4.18; N, 14.16.

Method B: Reduction with sodium borohydride and palladium-charcoal in dioxane

The 4-(2-nitrophenylthio)pyrazolone (400a, 2.0 g) in dioxane (80 ml) was reduced according to the general procedure (p. 245). Acidification of the yellow filtrate over ice with glacial acetic acid then dilution with ice-water (300 ml) yielded a pale-brown precipitate (1.5 g). When this precipitate was dissolved in ethanol, a small amount (0.15 g) of pale-brown precipitate, m.p. 208-11° was formed. The i.r. spectrum of this product was identical to that of the thiol (406) described above. On cooling, the filtrate deposited a dark-yellow crystalline product (0.42 g), m.p. 153-5° which was identified (i.r. n.m.r. and mixed m.p.) as the spiro(benzothiazoline)pyrazolone (403).

Method C: Reduction with iron and ferrous ammonium sulfate

To a heated solution of the 4-(2-nitrophenylthio)pyrazolone

(400a, 3.0 g) in ethanol (100 ml) was added 6.0 g of reduced iron followed by a solution of ferrous ammonium sulfate (1.8 g) in water (75 ml). The mixture was heated under reflux for two hours then filtered. The filtrate was evaporated to dryness and the dried residue was dissolved in hot absolute ethanol (30 ml) then refiltered. On cooling, 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) separated as white needles (1.9 g), m.p. 183-4°. Reported m.p. 181° (Angelini and Martani, 1955), 183-4° (Pound, 1970).

I.r. spectrum (nujol): 2100-3350, broad with maxima at 3145 and 3295 (OH and NH_2), 1625 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.21 (3H, s, CH_3); 6.3-8.0 (9H, m, aromatic protons); 7.43 (3H, br. s, exchanged with D_2O, NH_2 and pyrazolone proton).

Mass spectrum: See Fig. 13.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13.

Found: C, 64.91; H, 4.99; N, 13.80.

Method D: Reduction with zinc and ammonium chloride

(i) To a hot solution of the 4-(2-nitrophenylthio)pyrazolone (400a, 1.0 g) in 60% aqueous ethanol (100 ml) was added 0.2 g of ammonium chloride in water (10 ml). Zinc dust (1.0 g) was added and the mixture was refluxed for three hours under nitrogen. The reaction mixture was filtered and the solvent was evaporated *in vacuo*. The dried residue was dissolved in hot ethanol and refiltered. The filtrate immediately precipitated a yellow powder (0.09 g), m.p. 212-14° which was identified (i.r.) as the previously described (p.301) thiol (406). After this product was collected, the mother liquor slowly deposited the spiro(benzothiazoline)pyrazolone (403) as dark-yellow needles (0.46 g), m.p. 153-4°. Its i.r. spectrum was identical with that of an authentic sample prepared earlier.

(ii) When the above reduction was repeated in a mixture of tetrahydrofuran (50 ml) and water (30 ml), it yielded a small amount (0.04 g) of yellow powder, m.p. 210-2° identified as the thiol (406). On standing, the mother liquor deposited a second product (0.29 g), m.p. 152-3° which was found (i.r.) to be the spiro(benzothiazoline)pyrazolone (403).

(iii) Reaction (i) was repeated except that the mixture was stirred at room temperature for ten hours instead of heating under reflux. The filtered reaction mixture was evaporated *in vacuo* yielding a yellow residue which when crystallized from ethanol gave spiro[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (403) as golden-yellow needles (0.62 g), m.p. 153-4°.

Method E: Catalytic hydrogenation

(i) The title compound (1.0 g) in ethanol (250 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (~20 mg). Hydrogen was absorbed slowly and more catalyst (~10 mg) had to be added and the reaction mixture was heated to 45°. After the uptake of hydrogen ceased, the catalyst and the yellow precipitate formed during the reaction were removed by filtration. This precipitate was dissolved in 10% sodium hydroxide, filtered and the filtrate acidified with dilute hydrochloric acid yielding a yellow powder (0.11 g) m.p. 205-10° identified (i.r.) as the thiol (406). Concentration of the filtered reaction mixture yielded another quantity (0.03 g), m.p. 207-10° of the thiol (406). On standing, the mother liquor remaining after the removal of this product slowly deposited a pale-yellow solid (0.14 g), m.p. 151-2° which was found (i.r. and mixed m.p.) to be the spiro(benzothiazoline)pyrazolone (403).

(ii) The above reaction was repeated using "Parr" hydrogenation apparatus with initial pressure 49 p.s.i.. A small amount (0.07 g), of yellow solid was formed during the reduction; this was collected and identified (i.r.) as the 4-(2-mercaptophenylamino)pyrazolone (406). Evaporation of the filtered reaction mixture yielded a yellow residue which displayed absorption bands at 1700, 3300, 3270 and 3240 in its i.r. spectrum. This residue was partially soluble in dilute sodium hydroxide solution. The soluble portion, on acidification with acetic acid, yielded a small amount of white solid (0.09 g), m.p. 182-4° which was shown (i.r., mixed m.p.) to be the 4-(2-aminophenylthio)pyrazolone (416). The insoluble portion was crystallized from ethanol to yellow needles (0.23 g), m.p. 150-2° identified as the spiro(benzothiazoline)pyrazolone (403).

Reductions of 1,3-diphenyl-4-(2-nitrophenylthio)-2-pyrazolin-5-one (400b)

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution

Using the general procedure outlined on p. 245, a solution of the title compound (2.0 g) in 10% aqueous sodium hydroxide (50 ml) was reduced with catalyzed (10% Pd-C) sodium borohydride. Acidification of the filtrate with dilute acetic acid yielded a flocculent yellow solid. This crystallized from ethanol as a yellow solid (0.52 g), m.p. 211-12° which is identified as 1,3-diphenyl-4-(2-mercaptophenylamino)-2-pyrazolin-5-one (417). Reported (Pound, 1970), m.p. 181-4°

(Compound erroneously identified by this author).

I.r. spectrum (nujol): 2300-3400, br. with maxima at 3060 (OH and SH); 3360 (NH); 1627 (bonded C=O?) cm^{-1}.

Mass spectrum: See Fig. 14.

Accurate mass measurements: 359.1090, $C_{21}H_{17}N_3OS$ requires 359.1090; 341.0984, $C_{21}H_{15}N_3OS$ requires 341.0987.

Anal. Calcd. $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69.

Found: C, 70.03; H, 4.86; N, 12.14.

This compound was sparingly soluble in ethanol. When a dilute alcoholic solution was concentrated then cooled, dark-yellow needles, m.p. 185-6° separated. This was spiro[benzothiazoline-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (418). Reported (Pound, 1970) m.p. 183-4°.

I.r. spectrum (nujol): 3373 (NH); 1715 (C=O) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ5.0 (1H, br.s, NH); 6.5-3.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 23.

Accurate mass measurements: See Table 5.

Anal. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76.

Found: C, 70.51; H, 4.28; N, 11.55.

Method B: Reduction with iron and ferrous ammonium sulfate

A solution of ferrous ammonium sulfate (0.6 g) in water (25 ml) was added to a suspension of the 4-(2-nitrophenylthio)pyrazolone (400b, 0.1 g) and iron (2.0 g) in ethanol (80 ml). The mixture was heated under reflux for two hours, filtered, and evaporated to dryness leaving a black semi-solid which could not be crystallized.

Method C: Reduction with zinc and ammonium chloride.

(i) Ammonium chloride (0.2 g) in water (10 ml) was added to a solution of title compound (1.0 g) in 60% aqueous ethanol (70 ml). To this, zinc dust (1.0 g) was added and the mixture was stirred under nitrogen for ten hours at room temperature then filtered. The filtrate was evaporated *in vacuo*, dissolved in hot ethanol and refiltered. Cooling yielded golden-yellow needles (0.6 g), m.p. 185-6° identified (i.r. and mixed m.p. with authentic sample) as the spiro-(benzothiazoline)pyrazoline (418) described above (p.306).

(ii) The above reaction was repeated and the mixture was refluxed under nitrogen for two hours then filtered. Evaporation of the filtrate under vacuum yielded a yellow solid, the i.r. spectrum of which had a broad absorption between 2100 and 3400 and showed no carbonyl absorption around 1700 cm^{-1}. However, when this product was dissolved in ethanol and left to crystallize it gave dark-yellow needles, m.p. 185-6° which was shown to be the spiro(benzothiazoline)-pyrazolone (418).

Reduction of spiro[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1*H*-pyrazolin-5'-one)] (403)

A solution of the title compound (1.0 g) in a mixture of dioxane (15 ml) and 10% aqueous sodium hydroxide (15 ml) was reduced with sodium borohydride and palladium-charcoal following the general procedure (p. 245). The filtered reaction mixture was acidified over ice with dilute acetic acid and then diluted with water (50 ml). The pale-yellow precipitate was collected and dissolved in ethanol. On standing a yellow precipitate (0.13 g), m.p. 207-11° was formed. This was identified (i.r.) as the 4-(2-mercaptophenylamino)pyrazolone (406). Concentration of the mother liquor remaining after the removal of the above compound yielded yellow crystals (0.36 g), m.p. 151-2° the i.r. spectrum of which was identical with the title compound.

Reactions of 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-pyrazolin-5-one (406).

(1) Air Oxidation:

A sample (0.3 g) of the title compound was suspended in ethanol (15 ml) and left exposed to the atmosphere at room temperature for 48 hours. During this time, it entered solution; the yellow solution became dark-brown then dark-yellow needles (0.18 g), m.p. 153-4° slowly separated. This product was found (i.r., n.m.r. and mixed m.p.) to be the spiro(benzothiazoline)pyrazolone (403).

(2) Methylation:

a. Ethereal diazomethane was added, in excess, to a stirred, ice-cooled suspension of the title compound (1.0 g) in ether (30 ml). After about two hours, solubilization of products was complete but the solution was allowed to stand for a further ten hours at room temperature, then the rose-red solution was evaporated under vacuum leaving a reddish oily residue, which crystallized from methanol to yellow needles (0.58 g), m.p. 150-1°. Its infrared and n.m.r. spectra were identical to those of the previously identified spiro[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1_H_-pyrazolin-5'-one)] (403).

b. Dimethyl sulfate (1.0 ml) was added dropwise with stirring to an ice-cold solution of the 4-(2-mercaptophenylamino)-pyrazolone (406, 1.0 g) in 10% sodium hydroxide. After stirring for two hours, the resulting gummy residue was extracted with chloroform and the chloroform solution was washed with 10% sodium hydroxide then with water. Evaporation of the dried ($CaCl_2$) extract gave a brown solid which crystallized from ethanol yielding 2,3-dimethyl-4-(2-methylthiophenylamino)-1-phenyl-2-pyrazolin-5-one (408) as pale-brown needles (0.47 g), m.p. 161-2°.

I.r. spectrum (nujol): 3335 (NH); 1670 (C=O) cm^{-1}.

N.m.r. spectrum: ($CDCl_3$): δ2.14 (3H, s, C CH_3); 2.39 (3H, s, S CH_3); 3.03 (3H, s, N CH_3); 6.12 (1H, br. s, exchanged with D_2O, NH); 6.4-7.6 (9H, m, aromatic protons).

Mass spectrum: See Fig. 11.

Accurate mass measurements: 325.1240, $C_{18}H_{19}N_3OS$ requires 325.1249; 278.1287, $C_{17}H_{16}N_3O$ requires 278.1293.

Anal. Calcd. for $C_{18}H_{19}N_3OS$: C, 66.46; H, 5.85; N, 12.92.

Found: C, 66.83; H, 6.16; N, 12.68.

(3) Benzoylation:

was carried out according to the method described by Pound (1970). Benzoyl chloride (2.0 ml) was added dropwise, with stirring to an ice-cold solution of the title compound (1.0 g) in 10% sodium hydroxide (40 ml). Stirring was continued at room temperature for one hour then the resulting semi-solid was extracted with chloroform. Evaporation of the dried ($CaCl_2$) extract left a dark-yellow semi-solid which was difficult to crystallize. This was placed on a silica gel column and eluted with benzene/chloroform (1:2) yielding a fraction which, on evaporation, gave a brown solid (0.61 g). This was crystallized twice from benzene/petroleum ether (40-60°) and gave 4-[N-benzoyl-N-(benzoylthiophenyl)amino]-5-benzoyloxy-3-methyl-1-phenylpyrazole (414) as pale-brown solid, m.p. 104-7°. Reported

(Pound, 1970) m.p. 102-4° (Compound erroneously identified by this author).

I.r. spectrum (nujol): 1758 and 1679 (C=O) cm^{-1}.

Mass spectrum: See Fig. 12.

Accurate mass measurements: 609.1724, $C_{37}H_{27}N_3O_4S$ requires 609.1723.

Anal. Calcd. for $C_{37}H_{27}N_3O_4S$: C, 72.89; H, 4.46; N, 6.89.

Found: C, 72.67; H, 4.51; N, 6.99.

(4) Acetylation:

a. A suspension of the 4-(2-mercaptophenylamino)pyrazolone (406, 0.5 g) in acetic anhydride (5 ml) was heated under reflux for fifteen minutes. The resulting red solution was poured, with stirring, into ice-cold 5% sodium hydroxide solution (30 ml) giving a brown precipitate. This was extracted with chloroform and the chloroform extract was washed with 10% sodium carbonate then with water and dried ($CaCl_2$). Evaporation of this extract yielded a brown oil which crystallized from ethanol into dark-yellow crystals (0.19 g), m.p. 150-1°, the i.r. of which was identical with the spiro(benzothiazoline)pyrazolone (403).

b. Acetyl chloride (2.0 ml) was added to a suspension of the 4-(2-mercaptophenylamino)pyrazolone (406, 0.5 g) in benzene (15 ml) and the mixture was refluxed for one hour then evaporated under vacuum. Crystallization of the dark-red semi-solid yielded the spiro(benzothiazoline)pyrazolone (403) as dark-yellow needles (0.22 g), m.p. 153-4°.

c. The 4-(2-mercaptophenylamino)pyrazolone (406, 0.5 g) was added to a cold mixture of pyridine (5.0 ml) and acetic anhydride

(5.0 ml) and stirred for fifteen minutes. The resulting solution was added with stirring to ice-cold water (40 ml) giving a yellow precipitate (0.46 g), m.p. 104-10° identified as 5-acetyloxy-3-methyl-4-(2-acetylthiophenylamino)-1-phenylpyrazole (415). This compound was insoluble in dilute sodium-hydroxide solution.

I.r. spectrum (nujol): 3368 (N—H); 1788 ($OCOCH_3$); 1720 ($SCOCH_3$) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.15 (3H, s, CH_3); 2.22 (3H, s, CH_3); 2.44 (3H, s, CH_3); 6.2 (1H, br. s, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: 381 (M^+, 3%), 339 (17%), 321 (3%), 297 (20%), 295 (64%), 279 (30%), 267 (75%), 135 (100%).

Anal. Calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.97; H, 5.02.

Found: C, 63.53; H, 4.89.

Attempts to crystallize the above compound from ethanol yielded, after about 24 hours standing, a yellow crystalline solid m.p. 152-4° which was found (i.r.) to be the spiro(benzothiazoline)pyrazolone (403).

General procedure for the preparation of spiro[(3-substituted-3,4-dihydro-2H-1,4-benzothiazine)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-ones)] (419)

Equimolar quantities of 4-(2-aminophenylthio)-3-methyl 1-phenyl-2-pyrazoline-5-one (416) and the appropriate aldehyde were heated, under reflux, in ethanol for one to two hours. The reaction of (416) and acetone was carried out in n-butanol and heating was prolonged to 24 hours. Most products crystallized from the reaction solvent on cooling.

Table 8 collects the physical constants and elemental analyses of the compounds prepared by this method. The i.r. spectra of all these compounds displayed N—H absorption bands around 3400 and C=O bands around 1700 cm^{-1}. Their n.m.r. spectra (in DMSO-d_6) had signals ascribable to the pyrazolone C-3 methyl group (around δ2.0), the aromatic protons and the different substitutents at C-3 of the dihydrobenzothiazine ring. In addition, each spectrum (except that of the 3,3-dimethyl derivative 419n) contained a one proton signal near δ4.8 $(-\overset{|}{C}\underline{H}R)$ and a deuterium-exchangeable N—H signal of variable chemical shift. Both the pyrazolone C-3 methyl group and the hydrogen at C-3 of the dihydrobenzothiazine ring appeared as two signals separated by from 3 Hz (419e, R'=*p*-hydroxyphenyl) to 14 Hz (419b, R'=CH_2CH_3). This separation was absent in compounds 419c, R'=$COCH_3$ and (419n, R=R'=CH_3). The mass spectra of some of these compound were recorded (see Fig. 15 and 16 and Table 4).

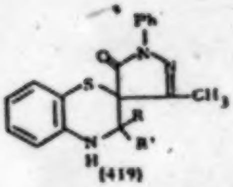
Attempts to separate the positional isomers of compound 419l (R=H, R'=*o*-nitrophenyl) by fractional crystallization failed.

Acetylation of two spiro(dihydrobenzothiazine)pyrazolones:

The spiro(dihydrobenzothiazine)pyrazolones, 419h (R=H, R'=2,5-dimethoxyphenyl) and 419e (R=H, R'=*p*-hydroxyphenyl) were acetylated by heating with acetic anhydride for 15 minutes. Compound 419h produced a monoacetyl derivative, m.p. 214-5°.

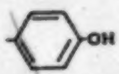
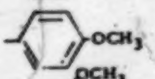
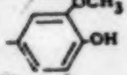
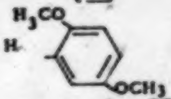
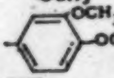
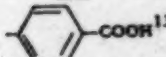
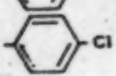
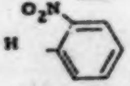
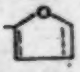
I.r. spectrum (nujol): 1665 (amide C=O); 1708 (lactam C=O) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ1.0 (3H, s, C—CH_3); 2.22 (3H, s, $COCH_3$); 3.38 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 6.67-8.2((13H, m, C_3—H and aromatic protons).



(419)

Table 8: Elemental analyses and physical properties ...etc. of the spiro(dihydrobenzothiazoline)-pyrazolones (419a-n).

Compound	R	R'	m.p. °C	% Yield	Molecular formula	Analyses % Calcd. C	Analyses % Calcd. H	Analyses % Calcd. N	Analyses % Found C	Analyses % Found H	Analyses % Found N
a	H	CH_3	149-50	76	$C_{18}H_{17}N_3OS$	66.84	5.29	12.99	66.63	5.44	12.75
b	H	C_2H_5	118-20	88	$C_{19}H_{19}N_3OS$	67.61	5.68	12.45	67.32	5.64	12.25
c	H	$COCH_3$	144-5	77	$C_{19}H_{17}N_3O_2S$	64.93	4.87	11.95	64.67	4.94	12.24
d	H	Ph	157-8	90	$C_{23}H_{19}N_3OS$	71.66	4.97	10.90	72.02	5.05	11.3
e	H	 OH	225-7	65	$C_{23}H_{19}N_3O_2S$	68.80	4.77	10.46	68.75	4.89	10.56
f	H	 OCH3	137-8	66	$C_{24}H_{21}N_3O_2S$	69.37	5.09	10.11	69.09	5.09	9.72
g	H	 OCH3 OH	172-3	63	$C_{24}H_{21}N_3O_3S$	66.81	4.91	9.74	66.82	4.78	9.95
h	H	 H3CO OCH3	129,30	90	$C_{25}H_{23}N_3O_3S$	67.39	5.20	9.43	67.36	5.56	9.18
i	H	 OCH3 OCH3	185-6	86	$C_{25}H_{23}N_3O_3S$	67.39	5.20	9.43	67.57	5.30	9.22
j	H	 COOH	134-5	84	$C_{24}H_{19}N_3O_3S$	67.10	4.46	9.80	67.31	4.29	9.61
k	H	 Cl	150-1	72	$C_{23}H_{18}ClN_3OS$	65.85	4.32	10.01	65.86	4.46	10.12
l	H	 O2N	187	92	$C_{23}H_{18}N_4O_3S$	64.17	4.21	13.01	64.31	4.29	13.09
m	H	 O	139-40	65	$C_{21}H_{14}N_3OS$	67.17	4.56	11.21	66.84	4.71	11.10
n	CH_3	CH_3	155-6	61	$C_{19}H_{19}N_3OS$	67.61	5.68	12.45	67.61	5.61	12.36

Anal. Calcd. for $C_{27}H_{25}N_3O_3S$: C, 68.76; H, 5.34; N, 8.91.

Found: C, 68.98; H, 5.69; N, 9.03.

Compound 419e gave a diacetylated product, m.p. 183-4°.

I.r. spectrum (nujol): 1768 (ester C=O); 1710 (lactam C=O); 1674 and 1660, doublet (amide C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ0.98 (3H, s, C–CH_3); 2.14 (3H, s, $OCOCH_3$); 2.22 (3H, s, N–$COCH_3$); 6.6 (1H, s, CH); 7.0-8.2 (13H, m, aromatic protons).

Anal. Calcd. for $C_{27}H_{23}N_3O_4S$: C, 66.79; H, 4.77; N, 8.65.

Found: C, 66.88; H, 4.72; N, 8.30.

Condensation of 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) with formaldehyde, salicylaldehyde and 2,4-dihydroxybenzaldehyde.

A. Formaldehyde (1.0 ml of 45% solution in water) was added to a hot solution of the title compound (0.5 g) in methanol (5 ml) and the mixture was refluxed for one hour. Evaporation of the solvent gave a colorless oil which would not crystallize.

I.r. spectrum (thin film): 1710 (C=O) cm^{-1}; no NH or OH absorption.

B. A mixture of the title compound (1.0 g) and salicylaldehyde (0.41 g) in ethanol (30 ml) was heated under reflux for one hour during which time a yellow precipitate was formed. Crystallization of this precipitate from ethanol yielded a yellow solid (1.15 g), m.p. 232-3° identified as 4-[2-(*o*-hydroxybenzylidene)aminophenylthio]-3-methyl-1-phenyl-2-pyrazolin-5-one (425a).

I.r. spectrum (nujol): 2000-3300, broad (OH); 1612 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.2 (3H, s, CH_3); 5.4 (1H, s, CH);

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6.3-8.0 (13H, m, aromatic protons and pyrazolone proton); 8.82 (1H, br. s, exchanged with D_2O, OH); 9.84 (1H, br. s, exchanged with D_2O, OH).

Anal. Calcd. for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.07.

Found: C, 66.47; H, 4.12; N, 9.66.

III. 1-HYDROXY-2-PHENYL-1,2-DIHYDROPYRIDINE AND BENZOYL DERIVATIVE

1-Hydroxy-2-phenyl-1,2-dihydropyridine (255)

This compound was prepared by the interaction of pyridine 1-oxide (2.8 g) and phenylmagnesium bromide (7.9 g) in tetrahydrofuran (15 ml) according to the method described by Kato and Yamanaka (1965). Crystallization from benzene yielded the title compound as pale-yellow needles (3.1 g), m.p. 132° as reported (Kato and Yamanaka, 1965).

I.r. spectrum (nujol): 3400-2400 (N—OH) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): The N-OH proton appeared at $\delta 8.72$ and disappeared when D_2O was added.

Mass spectrum: See Fig. 24.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09.
Found: C, 76.26; H, 6.18; N, 8.12.

1-Benzoyloxy-2-phenyl-1,2-dihydropyridine (437)

Was prepared according to the method of Kato *et al* (1967) in 90% yield, m.p. 79-80°. Reported m.p. 78.5-79.5°.

I.r. spectrum (nujol): 1755 (C=O) cm^{-1}.

Mass spectrum: See Fig. 24.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05.
Found: C, 77.71; H, 5.41; N, 5.06.

REFERENCES

Abramovitch, R. A., J. Chem. Soc., 1413 (1957).

Acheson, R. M., Adcock, B., Glover, G. M. and Sutton, L. E., J. Chem. Soc., 3367 (1960).

Acheson, R. M., Bolton, R. G. and Hunter, I., J. Chem. Soc. (C), 1067 (1970).

Acheson, R. M., Brookes, C. J. Q., Dearnaley, D. B. and Quest, B., J. Chem. Soc. (C), 504 (1968).

Adkins, H., "Reactions of Hydrogen", Univ. of Wisconsin press, 1937.

Akabori, Y., Chem. Abstr., 63, 16631a (1965).

Akagane, K., Allan, F. J., Allan, G. G., Friberg, T., Muircheartaigh, S. O. and Thomson, J. B., Bull. Chem. Soc. Japan, 42, 3204 (1969).

Alford, E. J., Hall, J. A., Rogers, M. A. T., J. Chem. Soc. (C), 1103 (1966).

Allan, F. J. and Allan, G. G., Chem. Ind., 1837 (1964).

Angelini, C. and Martani, A., Ann. chim. (Rome), 45, 156 (1955); Chem. Abstr., 50, 3416b (1956).

Askam, V. and Deeks, R. H. L., J. Chem. Soc., (C), 1243 (1968).

Baczynski, W., and Niementowski, S. V., Chem. Zentr., 73, 940 (1902).

Baker, A. W. and Harris, G. W., J. Amer. Chem. Soc., 82, 1923 (1960).

Bamberger, E., Ann., 424, 233 (1921); 441, 297 (1925).

Bankiewicz, Z., Ber., 22, 1396 (1889).

Bapat, J. B., Black, D. St. C., and Brown, R. F. C., in Advances in Heterocyclic Chemistry, vol. 10. Edited by A. R. Katritzky and A. J. Boulton, Academic Press Inc., New York, 1969, p. 199.

Baxter, I. and Swan, G. A., J. Chem. Soc., (C), 2446 (1967).

Beaumont, S. M., Handford, B. D., Jones, J. H. and Young, G. T., Chem. Commun., 53 (1965).

Becher, D., Sample, S., and Djerassi, C., Ber., 99, 2284 (1966).

Beckett, A. H. and Al-Sarraj, S., J. Pharm. Pharmacol., 24, 174 (1972).

Beckett, A. H. and Salami, M. A., J. Pharm. Pharmacol., 24, 900 (1972).

Bellamy, L. J., "Advances in Infrared Group Frequencies", Methuen and Co. Ltd., London, (1968).

Beynon, J. H., Lester, C. R. and Williams, A. E., J. Phys. Chem. 63, 1861 (1959).

Bhati, A., Johnstone, R. A. W. and Milliard, B., J. Chem. Soc. (C), 358 (1966).

Biehler, J. M. and Fleury J. P., Tetrahedron Letters 4227 (1968).

Biehler, J. M. and Fleury, J. P., Tetradron, 27, 3171 (1971).

Blout, E. R., Cohen, S. G. and Green, M., U.S. Pat. 2,843,481; Chem. Abstr., 52, 18044 (1958).

Blaise, E. E., Chem. Abstr., 8, 3012 (1914).

Blatt, A. H., J. Am. Chem. Soc., 56, 2774 (1934).

Bodendorf, K. and Raaf, H., Ann., 592, 26 (1955).

Bodendorf, K. and Towliati, H., Arch. Pharm., 298, 293 (1965).

Bogart, M. T. and Stull, A., in "Organic Syntheses", vol. 8, Edited by R. Adams, John Wiley and Sons, Inc., New York, 1928, p. 64.

Bonnett, R., Brown, R. F. C., Clark, V. M., Sutherland, I. O., and Todd, Sir A., J. Chem. Soc., 2094 (1959).

Bonnett, R. and McGreer, D. E., Can. J. Chem., 40, 177 (1962).

Bouchet, P., Elguero, J. and Jacquier, R., Tetrahedron, 22, 2461 (1966).

Boulton, A. J., Gray, A. C. G. and Katritzky, A. R., Chem. Commun., 741 (1966).

Boulton, A. J., Gripper Gray, A. C., and Katritzky, A. R., J. Chem. Soc., (B), 911 (1967).

Bowering, W. D. S., Clark, V. M. Thakur, R. S., and Todd, A., Ann., 669, 106 (1963).

Bowie, J.H., Cooks, R. G., Fisher, J. W. and Spotaswood, T. McL., Aust. J. Chem., 21, 2021 (1968).

Bowman, R. E. and Franklin, C. S., J. Chem. Soc., 1583 (1957).

Boyland, E., Manson, D. and Nery, R., J. Chem. Soc., 606,(1962).

Boyland, E. and Nery, R., Analyst, 89, 95 (1964); 89, 520 (1964a).

Brack, A., Belg. Pat. 617,180 (1962); Chem. Abstr., 59, 636 (1963).

Brady, O. L. and Day, J. N. E., J. Chem. Soc., 2258 (1923).

Brady, O. L. and Jakobovits, J., J. Chem. Soc., 767 (1950).

Brady, O. L. and Reynolds, C. V., J. Chem. Soc, 193 (1928); (1931).

Brown, C. W. and Rogers, M. A. T., Chem. Abstr., 55, 6598 (1961).

Brown, H. C., "Hydroboration", W. A. Benjamin Inc., New York, 1962, p. 242.

Brown, R. F. C., Clark, V. M., Lamchen, M., Sklarz, B. and Todd, Sir A., Proc. Chem. Soc., 169 (1959c).

Brown, R. F. C., Clark, V. M., Lamchen, M. and Todd, Sir A., J. Chem. Soc. 2116 (1959b).

Brown, R. F. C., Clark, V. M., Sutherland, I. O., and Todd, Sir A., J. Chem. Soc., 2109 (1959a).

Brown, R. F. C., Clark, V. M. and Todd, Sir A., J. Chem. Soc., 2105 2105, (1959); 2337 (1965).

Bursey, M. M. and Elwood, T. A., Org. Mass Spectrum., 1, 531 (1968).

Busch, M., Ber., 64, 1816 (1931).

Busch, M. and Kammerer, R., Ber., 63, 649 (1930).

Cable, J., Kagal, S. A. and MacLeod, J. K., Org. Mass Spectrom., 8, 301 (1972).

Calder, I. C., Creek, M. J., Williams, P. J., Funder, C. C., Green, C. R., Ham, K. N. and Tange, J. D., J. Med. Chem. 16, 499 (1973).

Cannon, J. G., Rose, J. G., Nerland, D. E. and Darko, L. L., J. Heterocycl. Chem., 6, 747 (1969).

Ciba Ltd., Netherlands pat. 6,515,833 (1966); Chem. Abstr., 65, 15388h (1966).

Clark, V. M., Sklarz, B. and Todd, Sir. A., J. Chem. Soc., 2123 (1959).

Clark-Lewis, J. W. and Ketekar, G. F., J. Chem. Soc., 2825 (1959).

Clougherty, L. E., Sousa, J. A. and Wyman, G. M., J. Org. Chem., 22, 462 (1957).

Colonna, M., Chem. Abstr., 30, 3420 (1936).

Colonna, M. and Bruni, P., Chem. Abstr., 61, 633 (1964).

Colonna, M. and Bruni, P., Gazz. Chim. Ital., 95, 1172 (1965); 97, 1569 (1967); 97, 1584 (1967a).

Colonna, M. and De Martino, U., Gazz. Chim. Ital., 93, 1183 (1963).

Colonna, M. and Monti, A., Gazz. Chim. Ital., 92, 1401 (1962).

Cope, A. C. and Trumbull, E. R., in "Org. Reactions", Edited by A. C. Cope, John Wiley, Inc., New York, Vol. 11, 1960 p. 317.

Cotter, J., J. Chem. Soc., 5491 (1964).

Coutts, R. T., Can. J. Pharm. Sci., 2, 27 (1967).

Coutts, R. T., J. Chem. Soc., 713 (1969).

Coutts, R. T., Barton, D. L., and Smith, E. M., Can. J. Chem., 44, 1733 (1966).

Coutts, R. T. and Edwards, J. B., Can. J. Chem., 44, 2009 (1966).

Coutts, R. T. and Hindmarsh, K. W., Can. J. Pharm. Sci., 1, 11 (1966).

Coutts, R. T., Hindmarsh, K. W., and Pound, N. J., Can. J. Chem., 44, 2105 (1966).

Coutts, R. T. and Malicky, J. L., Org. Mass Spectrom., 7, 985 (1973).

Coutts, R. T. and Mukherjee, G., Org. Mass Spectrom., 3, 63 (1970).

Coutts, R. T., Noble, D., and Wibberley, D. G., J. Pharm. Pharmacol., 16, 773 (1964).

Coutts, R. T., Peel, H. W., and Smith, E. M., Can. J. Chem., 43, 3221 (1965).

Coutts, R. T. and Pound, N. J., Can. J. Chem., 48, 1859 (1970).

Coutts, R. T. and Smith, E. M., Can. J. Chem., 45, 975 (1967).

Coutts, R. T. and Wibberley, D. G., J. Chem. Soc., 4610 (1963).

Cox, J. R. and Dunn, M. F., Abstracts, 152nd meeting of the ACS S162, New York, September (1966).

Curtin, D. Y. and Engelmann, J. H., Tetrahedron Letters, 3911 (1968).

Curtius, T. and Mayer, M., J. Prakt. Chem., 76, 369 (1907); Chem. Abstr., 2, 1285 (1908).

Delpierre, G. R. and Lamchen, M., J. Chem. Soc., 4693 (1963).

Delpierre, G. R. and Lamchen, M., Quart. Rev. (London), 19, 329 (1965).

Deorha, D. S. and Soreen S. P., J. Indian Chem. Soc., 41, 793 (1964).

Desmarchelier, J. M. and Johns, R. B., Org. Mass Spectrom., 2, 37 (1969a); 2, 697 (1969b).

DeStevens, G., Brown, A. B., Rose, D., Chernov, H. I. and Plummer, A. J., J. Med. Pharm. Chem., 10, 211 (1967).

Dewar, M., "Electronic Theory of Organic Reactions", Oxford Univ. press, 1949, p. 225.

Dibeler, V., Franklin, J. and Reese, J., J. Amer. Chem. Soc., 81, 68 (1959).

Diels, O., Ber., 51, 965 (1918).

Diels, O. and Solomon, C., Ber., 52, 43 (1919).

Diels, O. and Van Der Leeden, Ber., 38, 3357 (1905).

Dobeneck, H. V. and Lehmerer, W., Ber., 90, 161 (1957); Chem. Abstr., 51, 17884i (1957).

Draper, P. M. and MacLean, D. P., Can. J. Chem., 46, 1499 (1968).

Edwards, J. T. and Whiting, J., Can. J. Chem., 49, 3502 (1971).

Elias, D. J. and Gillis, R. G., Aust. J. Chem., 19, 251 (1966).

Elguero, J., Jacquier, R. and Tizane, D., Tetrahedron, 27, 133 (1971).

El-Kholy, I E. S., Rafla, F. K. and Soliman, G., J. Chem. Soc., 1857 (1957).

Eloy, F., J. Org. Chem., 26, 952 (1961).

Elsworth, J. F. and Lamchen, M., J. Chem. Soc., (C), 1477 (1966); 2423 (1968).

Exner, E., Coll. Czech. Chem. Comm., 20, 202 (1955).

Feigl, F., "Spot Tests in Organic Analysis", translated by R. E. Oesper, 7th ed. (English), Elsevier, Amsterdam, 1966, p. 338.

Feldman, A. M. and Hoffmann, A. K., French Pat. 1,360,030 (1964); Chem. Abstr., 61, 13289d (1964).

Field, G. F., Zally, W. J., and Sternbach, L. H., Tetrahedron Letters, 2609 (1966).

Fischer, E. and Hütz, H., Ber., 28, 585 (1895).

Forrester, A. R. and Thomson, R. H., J. Chem. Soc., 5632 (1963).

Freeman, J. P., J. Amer. Chem. Soc., 80, 5954 (1958).

Freeman, J. P., J. Org. Chem., 27, 2881 (1962).

Freeman, J. P., Chem. Rev., 73, 283 (1973).

Freeman, J. P. and Gannon, J. I., J. Heterocycl. Chem., 3, 544 (1966).

Freeman, J. P. and Gannon, J. J., J. Org. Chem, 34, 194 (1969).

Freeman, J. P. and Hansen, J. F., Chem. Commun., 961 (1972).

Freeman, J. P., Gannon, J. J. and Surbey, D. L., J. Org. Chem., 34, 187 (1969).

Fries, K. and Reity, H., Ann., 527, 38 (1937).

Gabriel, S. and Gerhard, W., Ber., 54, 1067 (1921).

Gabriel, S. and Gerhard, W., and Wolter, R., Ber., 56, 1024 (1923).

Gambarian, S., Ber., 588,1775 (1925)

Gambarian, S., and Kazaryan, L., J. Gen. Chem. (U.S.S.R.), 3, 222 (1933).

Gassman, P. G., Campbell, G. and Frederick, R., J. Amer. Chem. Soc., 90, 7377 (1968).

Gassman, P. G. and Campbell, G. A., Chem. Commun., 1437 (1971).

Gassman, P. G. and Hartman, G. D., Chem. Commun., 853 (1972).

Gilbert, J. N. T., and Millard, B. J., Org. Mass Spectrom., 2, 17, (1969).

Goering, H. L., Greiner, R. W. and Shoan, M. F., J. Amer. Chem. Soc., 83, 1391 (1961).

Gortinskaya, T. V., Nyrkova, V. G., Savitskaya, N. V., Shchukina, M. N., Polezhaeva, A. I., and Nashkouskii, M. D., Pharm. Chem. J. (U.S.S.R.), 279 (1973).

Graham, W., J. Amer. Chem. Soc., 84, 1063 (1962).

Grindstedvaerket, A., French pat. 1,482,641 (1967); Chem. Abstr., 68, 105261t (1968).

Gmelin, R. and Virtanen, A. J., Acta Chem. Scand., 16 1378 (1962).

Grove, J. F., Jeffs, P. W. and Rustidge, D. W., J. Chem. Soc., 1956 (1956).

Gutmann, H. R., Barry, E. J. and Malejka-Giganti, D., J. Nat. Cancer. Inst., 43, 287 (1969).

Habib, M. S. and Rees, C. W., J. Chem. Soc., 3371 (1960); 123 (1962).

Harden, A. and Okell, J., Chemical News, 83, 45 (1901).

Harris, C. and Tietz, H., Ann., 330, 237 (1904).

Hayashi, E. and Iijima, C., Yakagaku Zasshi, 82, 1093 (1962).

Hayashi, E., Ishiguro, E. and Enomota, M., Annual Meeting of Pharmac. Soc. Japan (1960).

Heller, H. E., Hughes, E. D., and Ingold, C. K., Nature, 168, 909 (1951).

Heller, G. and Wunderlich, P., Ber., 47, 2889 (1914).

Hendershot, L. C., and Forsaith, J., J. Pharmacol. Exp. Ther., 125, 237 (1959).

Henry, R. A. and Dehn, W. M., J. Amer. Chem. Soc., 72, 2280 (1950).

Hickinbottom, W. J., "Reactions of Organic Compounds", Longmans, London, 1959, p. 456.

Hinman, R. L., Elefson, R. D. and Campbell, R. D., J. Amer. Chem. Soc., 82, 3988 (1960).

Hinton, I. G. and Mann, F. G., J. Chem. Soc., 599 (1959).

Hirata, Y., Shimomura, O. and Eguchi, S., Tetrahedron Letters, 4 (1959).

Hodgson, H. H. and Hathaway, D. E., J. Chem. Soc., 538 (1944).

Hoffman-LaRoche, Netherlands pat. 6,515,498 (1966); Chem. Abstr., 65, 15406f (1966).

Houff, W. H., Hinsvark, O. N., Weller, L. E., Wittwer, S. H. and Sell, H. M., J. Amer. Chem. Soc., 76, 5654 (1954).

Hubacher, M. H. in "Organic Syntheses", vol. 15. Edited by C. R. Noller, John Wiley and Sons, Inc., New York, 1935, p. 45.

Huisgen, R., Grashey, R., Aufderhaar, E. and Kunz, R., Ber, 98, 642 (1965).

Ingold, C. K., "Structure and Mechanism in Organic Chemistry", Bell, London, 1953, p. 621.

Ingraffia, F., Gazz. Chim. Ital., 63, 175 (1933); Chem. Abstr., 27, 3710 (1933).

Ionescu, M., Katritzky, A. R. and Ternai, B., Tetrahedron, 22, 3227 (1966).

Irving, C. C., in "Metabolic Conjugation and Metabolic Hydrolysis", Edited by W. H. Fishman, Vol. I, Academic Press, New York, 1970, p. 53.

Irwin, S., Science, 136, 123 (1962).

Irwin, S., in "Animal and Clinical Pharmacological Techniques in Drug Evaluation", Eds. H. Nodine and R. E. Siegler, Year Book Med. Pubs., Philadelphia, 1964, p. 36.

Johns, S. R., Lamberton, J A., Occolowitz, J. L., Aust. J. Chem., 20, 1737 (1963).

Jones, L. W. and Major, R. T., J. Amer. Chem. Soc., 49, 1527 (1927)

Kamel, M., Allam, M. A. and Abou-Zeid, N. Y., Tetrahedron, 23, 1863 (1957).

Kato, T. and Yamanaka, H., J. Org. Chem., 30, 910 (1965).

Kato, T., Yamanaka, H., Adachi, T. and Hiranuma, H., J. Org. Chem., 32, 3788 (1967).

Katritzky, A. R., Quart. Rev. (London), 10, 395 (1956).

Katritzky, A. R. and Ambler, A. P., in "Physical Methods in Heterocyclic Chemistry", vol. II, Edited by A. R. Katritzky, Academic press, New York, 1963.

Katritzky, A. R. and Jones, R. A., J. Chem. Soc., 2947 (1960).

Katritzky, A. R. and Logowski, J. M., "Chemistry of Heterocyclic N-Oxides", Acad. Press, London, 1971, p. 108; 1971a, p. 406; 1971b, p. 422; 1971c, p. 153; 1971d, p. 269.

Katritzky, A. R. and Maine, F. W., Tetrahedron, 20, 299 (1964).

Kawaguchi, T., Matsubara, T. and Kato, H., Chem. Abstr., 66, 85529 (1967).

Kawana, M., Yoshioka, M., Miyaji, S., Kataoka, H., Omote, Y. and Sugiyama, N., Chem. Abstr. 63, 11479f (1965).

Kew, D. J. and Nelson, P. F., Aust. J. Chem., 15, 792 (1962).

Kliegl, A. and Brosamle, A., Ber., 69, 197 (1936).

Kliegl, A. and Fehrle, A., Ber., 47, 1629 (1914).

Kloetzel, M. C. and Pinkus, J. L., J. Amer. Chem. Soc., 80, 2332 (1958).

Kloetzel, M. C., Pinkus, J. L. and Washburn, R. M., J. Amer. Chem. Soc., 79, 4222 (1957).

Knorr, L. and Jodicke, F., Ber., 18, 2256 (1885).

Knorr, L., Ann., 236, 137 (1887).

Kohler, E. P. and Barrett, G. R., J. Amer. Chem. Soc., 46, 2105 (1924); 48, 1770 (1926).

Kohler, E. P. and Drake, N. L., J. Amer. Chem. Soc., 45, 2145 (1923).

Knunyants, J. L. and Bykhovskaya, E G., Chem. Abstr., 54, 20840d (1960).

Krajcinovic, M. and Vranjican, D., Chem. Abstr., 27, 319 (1933).

Kuhn, R. and Blau, W., Ann., 615, 99 (1958).

Laparola, G., Gazz. Chim. Ital., 75, 216 (1945).

Larsen, E., Qureshi, H. and Moller, J., Org. Mass Spectrom., 7, 89 (1973).

Layer, R. W., Chem. Rev., 63, 489 (1963).

Lehmann, F., Ber, 30, 2736 (1897).

Lehmstedt, K., Ber, 65, 999 (1932).

Lotlikar, P. D., Biochim. Biophys. Acta, 170, 468 (1968).

Lotlikar, P. D., Scribner, J. D., Miller, J. A. and Miller, E. C., Life Sci., 5, 1263 (1966).

Loudon, J. D. and Tennant, G., J. Chem. Soc., 3466 (1960); 3092 (1962); 4268 (1963).

Loudon, J. D. and Tennant, G., Quart. Rev. (London), 18, 389 (1964).

Loudon, J. D. and Wellings, I., J. Chem. Soc., 3462, 3470 (1960).

Luetzov, A. E., Hoffman, N. E. and Vercellotti, J. R., Chem. Commun., 301 (1966).

Luetzov, A. E. and Vercellotti, J. R., J. Chem. Soc. (C), 1750 (1967).

Macbeth, A. K. and Price, J. R., J. Chem. Soc., 1637 (1934); 111 (1936).

MacLeod, J., Becher, D. and Djerassi, C., J. Org. Chem., 31, 4050 (1966).

McCluskey, K. L., J. Amer. Chem. Soc., 44, 1573 (1922).

McKillop, A. and Zelesko, M. J., Tetrahedron Letters, 4945 (1968).

Maier, D. P., Happ, G. P. and Regan, T. H., Org. Mass. Spectrom., 2, 1289 (1969).

Major, R. T. and Dürsch, F., J. Org. Chem., 26, 1886 (1961).

Mamalis, P., Xenobiotica, 1, 569 (1971).

Mamalis, P., Green, J., Outred, D. J. and Rix, M., J. Chem. Soc., 3915 (1962); 1829 (1965).

Mamlock, L. and Wolffenstein, R., Ber, 33, 159 (1900).

Mansel, D. and Spiers, N. A., J. Chem. Soc., 3971 (1959).

Miller, L. L., Chem. Abstr., 63, 8154b (1965).

Miller, J. A., Cancer Res., 30, 559 (1970).

Miller, E. C., Lotikar, P. D., Pitot, H. C., Fletcher, T. L. and Miller, J. A., Cancer Res., 26, 2239 (1966).

Miller, E. C. and Miller, J. A., Ann. N.Y. Acad. Sci., 163, 731 (1969).

Miller, E. C. and Miller, J. A., in "Chemical Mutagens. Principles and methods for Their Detection", Edited by A. Hollender, vol. I, Plenum Press, New York, 1971, p. 83.

Minisci, F., *Galli, R. and Quilico, A, Tetrahedron Letters*, 785 (1963).

Mitsui, S. and Saito, H., Nippon Kagaku Zasshi, 82, 390 (1961).

Maffei, S. and Bettinetti, G. F., Ann. chim. (Rome), 46, 812 (1956).

Morimoto, H. and Oshio, H., Ann., 682, 212 (1965).

Mousseron-Canet, P. M. and Boca, J. P., Bull. Soc. Chim. France, 2704 (1965); 1296 (1967).

Müller, E. Zimmermann, G., J. Prakt. Chem., 111, 277 (1925).

Musierowicz, A., Niementowski, S. and Tomasik, Z., Chem. Abstr., 23, 1900 (1929).

Nakanishi, K., "Infrared Absorption Spectroscopy", Nankodo, Toyko, 1962, p. 42.

Narang, K. S., Ray, J. N. and Singh, A., J. Indian Chem. Soc., 11, 427 (1934).

Neadle, D. J. and Politt, R. J., J. Chem. Soc. (C), 1764 (1967).

Nery, R., Analyst, 91, 388 (1966).

Newman, G. A. and Pauwels, P. J. S., Tetrahedron, 25, 4605 (1969).

Niementowski, S., Ber, 20, 1874 (1887); 25, 860 (1892); 32, 1456 (1899); 43, 3012 (1910).

Nietzki, R. and Braunschweigh, E., Ber, 27, 3381 (1894).

Nishiwaki, T., J. Chem. Soc. (B), 885 (1967).

Nyquist, R. A. and Potts, w. J., Spectrochimica Acta, 7, 514 (1959).

Nystrom, R. F. and Berger, R. A., J. Amer. Chem. Soc., 80, 2896 (1958).

Ochiai, E. and Arima, K., Chem. Abstr., 44, 1502 (1950).

Ohta, A. and Ochiai, E., Chem. Pharm. Bull. (Tokyo), 10, 1260 (1962).

Pachter, I. J. and Kloetzel, M. C., J. Amer. Chem. Soc., 73, 4958 (1951)

Passerini, M. and Rangi, G., Gazz. Chim Ital., 66, 684 (1936); Chem. Abstr., 31, 3484 (1937).

Paquette, L. A., J. Org. Chem., 27, 2870 (1962).

Paquette, L. A., J. Amer. Chem. Soc., 87, 1407, (1967).

Pavlova, L. V. and Rachinskii, F. Y., Chem. Abstr. 69, 105471g (1968).

Pelz, W., Püschel, W., Schellenberger, H. and Löffler, K., Angew. Chem., 72, 967 (1960).

Petracek, F. J., United States pat., 3,296,277 (1967); Chem. Abstr., 66, 55386y (1967).

Pollitt, R. J., Chem. Commun. 262 (1965).

Pound, N. J., Ph.D. Thesis, University of Alberta, Edmonton, Alberta, 1970.

Pylander, P. N., "Catalytic Hydrogenation over Platinum Metal", Academic press, 1967.

Quilico, A., in "The Chemistry of Heterocyclic Compounds", vol. 7. Edited by A. Weissberger, Interscience Publishers, New York, 1962, p. 229.

Refn, S., Spectrochim. Acta, 17, 40 (1961).

Reisssart, A., Ber., 29, 639 (1896); 30, 1030 (1897).

Robertson, G. R. and Evans, R. A., J. Org. Chem., 5, 142 (1940).

Rogers, M. A. T., J. Chem. Soc., 769 (1955).

Rogers, M. A. T., Nature, 177, 128 (1956).

Roncucci, R., Simon, J. J. and Lambellin, G., J. Chromatogr., 57, 410 (1971).

Rozantsev, E. G. and Neiman, M. B., Tetrahedron, 20, 131 (1964).

Rozantsev, E. G. and Shapiro, A., Chem. Abstr., 61, 7000f (1964).

Rugguli, B. H. and Casper, E, Helv. Chim. Acta, 22, 411 (1939).

Ruppert, W., Chem. Abstr., 54, 584C (1960).

Russell, D. W., Chem. Commun., 498 (1965).

Sammes, P. G., J. Chem. Soc., 6608 (1965).

Schubert, W. M. and Sweeney, W. A., J. Amer. Chem. Soc., 77, 4172 (1955).

Schweizer, E. E. and Kopay, C. M., J. Org. Chem., 37, 1561 (1972).

Scott, F. L. and Lelor, F.J., Chem. Ind., 420 (1966).

Secareanu, S. and Lupas, I., Bull. Soc. Chim. France, 53, 1436 (1938).

Sharma, H. L. and Mukerji, S. K., *Bull. Chem. Soc. Japan*, 38, 1086 (1965).

Shimomura, O., *J. Chem. Soc. Japan*, 81, 179 (1960).

Shine, H. J., Fang, Li-Tzn, Mallory, H. E., Chamberlain, N. F. and Stehling, F., *J. Org. Chem.*, 28, 2326, (1936).

Siegmund, E. A., Cadmus, R. A. and Lu, G., *Proc. Soc. exp. Biol.* (N.Y.), 95, 729 (1957).

Singh, H. and Kapil, R. S., *J. Org. Chem.*, 25, 657 (1960).

Snow, G., *J. Chem. Soc.*, 2588 (1954).

Spiro, V. and Vaccaro, G. C., *Ann. Chim. (Rome)*, 49, 2075 (1959); *Chem. Abstr.*, 54, 16443 (1960).

Stacy, G. W., Ettling, B. V. and Papa, A. J., *J. Org. Chem.*, 29, 1537 (1964).

Stacy, G. W., Wollner, T. E. and Oakes, T. R., *J. Heterocyc. Chem.*, 3, 51 (1966).

Sternbach, L. H. and Reeder, E., *J. Amer. Chem. Soc.*, 26, 1111 (1961).

Stöhrer, G., *Biochemistry*, 11, 4844 (1972).

Stöhrer, G. and Brown, G. B., *Science*, 167, 1622 (1970).

Stolle, R. and Thöma, J., *J. Prakt. Chem.*, 73, 288 (1906).

Sulkowski, T. S. and Childress, S. J., *J. Org. Chem.*, 28, 2150 (1963).

Sundberg, R. J., *J. Org. Chem.*, 30, 3604 (1965).

Sundberg, R. J., "*The Chemistry of Indoles*", Acad. Press, New York, 1970.

Takahashi, S. and Kano, H., *Chem. and Pharm. Bull. (Tokyo)*, 11, 1375 (1963); 12, 282 (1964); 14, 1219 (1966).

Tanida, H., *Chem. and Pharm. Bull. (Tokyo)*, 7, 887 (1959).

Tani, H., Oguni, N. and Araki, T., *Bull. Chem. Soc. Japan*, 37, 1245 (1964).

Tatematsu, A. and Goto, T., *J. Pharm. Sci. (Japan)*, 85, 631 (1965).

Tatematsu, A., Inoue, S. and Goto, T., *Tetrahedron Letters*, 4609 (1966).

Tartakovskii, V. A., Luk'yanov, O. A. and Novikov, S. S., *Chem. Abstr.*, 69, 1778 (1968).

Taylor, E. C. and Garcia, E. E., J. Amer. Chem. Soc., 86, 4721 (1964).

Taylor, E. C. and Kalenda, N. W., J. Org. Chem., 18, 1755 (1953).

Thesing, J. and Mayer, H., Ber., 89, 2159 (1956).

Thesing, J. and Mayer, H., Ann., 609, 46 (1957).

Thesing, J. and Sirrenberg, W., Ber, 91, 1979 (1958); 92, 1748 (1959).

Thuijl, J., Klebe, K. J. and Van Houte, J. J., Org. Mass Spectrom., 3, 1549 (1970).

Twomey, D., Chem. Abstr., 50, 340 (1956).

Tyler, J. M., J. Chem. Soc., 203 (1955).

Vinogradov, S. N. and Linnell, R. H., "Hydrogen Bonding", Van Nostrand Reinhold Corp., New York, 1971.

Vis, B., Rec. trav. chim., 58, 847 (1939).

Volkamer, K., Baumgärtel, H. and Zimmermann, H., Angew. Chem. internat. Edit., 6, 947 (1967).

Volkamer, K. and Zimmermann, H., Ber, 102, 4177 (1969).

Volodarsky, L. B., Lisack, A. N., Koptyug, V. A., Tetrahedron Letters, 1565 (1965).

Vul'fson, N. S. and Zhurin, R. B., J. Gen. Chem. (U.S.S.R.), 976 (1962).

Wahl, G. H., Org. Mass Spectrom, 3, 1349 (1970).

Weil, J. T., J. Chromatog., 36, 381 (1968).

Weisburger, J. H. and Weisburger, E. K., Pharmacol. Rev, 25, 1 (1973).

Wenick, W. and Wolffenstein, R., Ber, 31, 1560 (1898).

Wieland, H., Ber., 42, 803 (1909).

Wiley, R. H. and Wiley, P., "Pyrazolones, Pyrazolidones, and Derivatives", Interscience Publishers, New York, 1964.

Winterfeldt, E. and Krohn, W., Ber, 102, 2336 (1969).

Witkop, B., J. Amer. Chem. Soc., 78, 12873 (1956).

Witkop, B. and Patrick, J. B., J. Amer. Chem. Soc., 74, 3861 (1952).

Wölcke, Uwe, Birdsall, J. M., and Broun, G. W., Tetrahedron Letters, 10, 785 (1969).

Wright, J. B., J. Org. Chem., 29, 1620 (1964).

Young, G. T. and Handford, B. O., Brit. pat. 1,085,916 (1967); Chem. Abstr., 69, 27792 w (1968).

Yukawa, Y., J. Chem. Soc. Japan, 71, 547 (1950).

Zeeh, B. and Metzger, H. in "Houben-Wehl Methoden der Organischen Chemie", Edited by E. Mullor, Vol. XI, Stickstoffe Verbindung, Stuttgart, 1971, p. 1091.

Zincke, T. and Schwarz, P., Ann., 311, 329 (1900).

Zinner, G., Chem. Abstr., 51, 8087 (1957).

Zinner, G., Angew. Chem., 69, 204 (1957a).

Zinner, G., Ber., 91, 302 (1958); 99, 1292 (1966).

Zinner, G., Arch. Pharm. 291, 7 (1958a).

Zinner, G. and Dueerkop, E., Arch. pharm., 301, 776 (1968); Chem. Abstr. 70, 37641f (1969).

Zinner, G. and Kliegel, W., Ber, 99, 895 (1966).

Zinner, G. and Kliegel, W., Arch. Pharm., 299, 166 (1966a).

Zinner, G. and Moll, R., Ber, 1292 (1966).

Zinner, G. and Ritter, W., Angew. Chem., 74, 217 (1962).

Zinner, G., Ritter, W. and Kliegel, W., Pharmazie, 20, 291 (1965).